Radiologist Performance in the Detection of Lung Cancer using Computed Tomography

Badera Al Mohammad[1], Stephen Hillis[2] and Patrick Brennan[3]

[1] The University of Sydney
[2] University of Iowa
[3] The University of Sydney, Australia

Background: Lung cancer, the leading cause of cancer death around the world, can be survived if early detection through screening programs occurs. Radiologist performance plays a pivotal role in lung cancer detection.

Aim: To measure the level of radiologists' performance in lung cancer detection in Jordan. As a secondary aim we explore radiologists' detection performance in specialized and non-specialized centers.

Materials and Methods: The study was approved by the institutional review board of The University of Sydney. Informed consent was obtained from all the participating radiologists. Thirty radiologists with varying experience levels (median = 7 years) read sixty chest computed tomography (CT) scans. Thirty cases had surgically or biopsy-proven lung cancer and the remaining thirty were cancer-free cases. The cancer cases were validated by four expert radiologists who located the malignant lung nodules. Reader performance was evaluated by calculating sensitivity, location sensitivity, specificity, and area under the receiver operating characteristic curve (AUC). In addition, sensitivity at fixed specificity = 0.794 was computed from each reader's estimated receiver operating characteristic curve.

Results: The radiologists had a mean sensitivity of 0.749, sensitivity at fixed specificity of 0.744, location sensitivity of 0.666, specificity of 0.81 and AUC of 0.846. Radiologists in the specialized and non-specialized cancer centers had the following (specialized, non-specialized) pairs of values: sensitivity = (0.80, 0.719); sensitivity for fixed 0.794 specificity = (0.752, 0.740); location sensitivity = (0.712, 0.637); specificity = (0.794, 0.82) and AUC = (0.846, 0.846).

Conclusion: The estimated efficacy of radiologists in our study was comparable to estimates from other studies. In secondary analysis, receiver-operating-curve outcomes were similar for specialized and non-specialized center radiologists, suggesting that the two groups have similar discriminatory ability and that the observed higher sensitivity and lower specificity for specialized-center radiologists can be predominantly attributed to them being less conservative in interpreting case images.

The mammographic density of Indigenous women attending breast screening in the Northern Territory

Kriscia Tapia[1], Mark McEntee[1], Gail Garvey[2,1], Mary Rickard[1], Lorraine Lydiard[3] and Patrick Brennan[1]

[1] University of Sydney
[2] Menzies School of Health Research
[3] BreastScreen Northern Territory

Background: The burden of breast cancer is not shared equally across groups of women in Australia. Whilst breast cancer incidence is lower for Indigenous women, they face poorer outcomes with higher rates of death, younger onset age, more advanced tumours at diagnosis, and lower participation in breast screening compared with other Australians. Research into breast cancer and Indigenous women has steadily grown in the last 30 years however there remains scant information around risk factors. Breast density, an important independent risk factor for breast cancer, has been studied broadly in non-Indigenous women but not to a similar extent within Indigenous women.

Aims: To compare the mammographic densities and other characteristics of Indigenous and non-Indigenous women screened in Australia's Northern Territory.

Methods: Population screening program data of Indigenous (n = 857) and non-Indigenous women (n = 3236) were used. Mann-Whitney U test compared ages at screening and Chi-squared tests compared personal (age, screening attendance, remoteness, language, hormone replacement therapies, family history of breast cancer) and clinical information (symptoms, density, radiological finding). Logistic regression analysis was used for density groupings. OR and 95% CI were calculated for multivariate association for density.

Results: Mammographic density was lower amongst Indigenous women ($P<0.001$). For non-Indigenous women higher density was associated with younger age (OR 2.4, 95% CI 2.1-2.8), recall to assessment (OR 2.2, 95% CI 1.6-3.0), family history of breast cancer (OR 1.4, 95% CI 1.2-1.6), English-speaking background (OR 1.4, 95% CI 1.2-1.6), and residence in remote areas (OR 1.2, 95% CI 1.1-1.4). For Indigenous women density was associated with younger age (OR 2.7, 95% CI 2.0-3.5; $P<0.001$), and recall to assessment (OR 2.3, 95% CI 1.4-3.9; $P<0.05$).

Conclusion: Significant differences between Indigenous and non-Indigenous women were found. There were more significant associations for dense breasts for non-Indigenous women than for Indigenous women.

Advanced cancer patient perspectives on consenting to molecular tumour profiling: A qualitative study

Megan Best[1], Nicole Bartley[2], Chris Jacobs[3], Ilona Juraskova[4], Ainsley Newson[5], Jacqueline Savard[6], Bettina Meiser[7], Mandy Ballinger[8], David Thomas[8], Barbara Biesecker[9] and Phyllis Butow[10]

[1] PoCoG, Sydney Health Ethics, University of Sydney
[2] PoCoG, University of Sydney
[3] UTS
[4] School of Psychology, The University of Sydney
[5] Sydney Health Ethics, University of Sydney
[6] Deakin University
[7] UNSW Sydney
[8] Garvan Institute for Medical Research
[9] Research Triangle Institute
[10] University of Sydney

Background: Molecular tumour profiling (MTP), which aims to link molecular targets in tumours to cognate therapies, has entered clinical practice. However, little is yet known about the ethical, psychosocial and behavioural implications of MTP. The Molecular Screening and Therapeutics program is recruiting 1,000 patients with an advanced, solid, rare cancer to undertake MTP and, if an actionable variant is found, participate in a suitable therapeutic trial if available.

Aim: The current mixed methods psychosocial sub-study (PiGeOn) aims to explore participants' understanding, experiences and views regarding MTP at three timepoints: after giving consent, after receiving results, and at 5 months follow-up. Baseline qualitative results are reported here.

Methods: Purposive sampling is used to ensure diversity in cancer types and demographics. PiGeOn participants participate in a semi-structured interview. Framework analysis is employed to determine themes.

Results: Data collection is ongoing. 16 patients have participated, aged 41 to 77 years. Participants' motivations include: fear of death, trust in their oncologist, need for control and a sense of 'nothing lost'. Desperation and fear of dying dominate motivation, but participants also value being able to help others in a similar situation, and the chance to benefit other family members. Participants tolerate uncertainty, hope for reduced prognostic uncertainty, but fear loss of hope if no actionable result is found (the most likely outcome). They often lack understanding, but trust the science of MTP and the research process.

Conclusion: This is one of few studies to explore the experiences of people who have undergone MTP and will be the first Australian study to do this longitudinally. Identifying new treatment options overshadows broader and familial implications of genetic testing in this population. This increases the difficulty of supporting informed consent and shared decision-making in MTP testing. The current data will inform future policy and practice.

Young cancer patient perspectives on undertaking whole genome sequencing: A qualitative study

Megan Best[1], Nicole Bartley[2], Chris Jacobs[3], Ilona Juraskova[4], Ainsley Newson[5], Jacqueline Savard[6], Bettina Meiser[7], Mandy Ballinger[8], David Thomas[8], Barbara Biesecker[9] and Phyllis Butow[10]

[1] PoCoG, Sydney Health Ethics, University of Sydney
[2] PoCoG, University of Sydney
[3] UTS
[4] School of Psychology, The University of Sydney
[5] Sydney Health Ethics, University of Sydney
[6] Deakin University
[7] UNSW Sydney
[8] Garvan Institute for Medical Research
[9] Research Triangle Institute
[10] University of Sydney

Background: Whole genome sequencing (WGS) is moving into clinical practice, with the goals of identifying gene variants that increase individuals' risk of disease and guiding prevention strategies. Little is yet known about the ethical, psychosocial and behavioural implications of WGS. The Genetic Cancer Risk in the Young Study is recruiting 1,000 young cancer patients and blood relatives to undertake WGS to investigate heritable genetic disease drivers

Aim: The current mixed methods psychosocial sub-study (PiGeOn) aims to explore participants' motivations, understanding, experiences and views about WGS longitudinally. Baseline qualitative results are reported here.

Methods: Transcribed, semi-structured interviews of purposively selected PiGeOn participants (to ensure varied cancer types and demographics) were analysed using Framework analysis.

Results: Data analysis of 18 patients (aged 32-78 years) interviewed to date found that participants' motivations include: seeking empowerment, opportunity, a sense of responsibility to family, solidarity with similarly-affected people, and curiosity. Participants viewed genomic information as: reducing uncertainty, offering protection, not to be feared, and important to act upon.. All participants desired meaningful information that could inform action, and balanced this against personal and community costs. Participants often lacked full understanding and desired lay-appropriate explanations; but they, but felt embarrassed to request these. Most trusted the science of WGS and the research process. All recognised their results could have implications for other family members, but family culture influenced the degree of consultation before individuals consented.

Conclusion: Participants saw WGS as an opportunity to reduce future risk. Participants hoped for actionable results. A cancer diagnosis may motivate patients and family members to be more active in managing their risk, but may need interventions to promote better understanding and communication within the family about WGS results. Most participants considered WGS to be beneficial and found the experience of testing to be positive.

The findings from this study will inform the introduction of whole genome sequencing into clinical oncology.

Controlled drug release from a liposomal delivery platform triggered by X-ray radiation

Wei Deng[1], Wenjie Chen[2], Sandhya Clement[2], Anna Guller[1,3,4], Zhenjun Zhao[2], Alexander Engel[5] and Ewa Goldys[3]

[1] Macquarie University
[2] macquarie university
[3] University of New South Wales
[4] ARC Centre of Excellence for Nanoscale BioPhotonics
[5] University of Sydney

Background: Liposomes consist of an aqueous core surrounded by a lipid bilayer similar to cell membranes, which facilitates cellular uptake of liposomes. Liposomes are usually biocompatible and biodegradable, which makes them suitable for drug delivery. However conventional liposomes are unsuitable for the on-demand content release, which limits their therapeutic utility.

Aim: We intend to develop triggerable liposomes that are able to release drugs in a more controlled manner. With its excellent tissue penetration depth, X-ray radiation explored in this work for liposome triggering offers both spatial targeting via standard radiotherapy approaches and triggered release of encapsulated contents from the liposomes once they are located at the target site.

Methods:

We designed X-ray triggered liposomes by co-embedding photosensitizers and gold nanoparticles (3-5 nm) inside a lipid bilayer. *In vivo* antitumour effect was evaluated by monitoring tumour development and body weight of xenograft mice bearing colorectal cancer and by conducting histological analysis of tumour tissues after the treatments.

Results: X-ray triggered liposomes were demonstrated to control colorectal tumour growth more effectively than other individual modality treatment conditions.

Conclusion: X-rays with the suitable energy can easily penetrate the human body, activating drug release in deep tissues once the X-ray triggered liposomes reach their target. This feature will open many new opportunities for biomedical research and clinical medicine, from triggered chemotherapy, through to enhanced photodynamic therapy which currently suffers from limited penetration depth of illumination light. Additionally, the strategy described here has been designed to be compatible with future clinical translation. The materials and approaches used in this study, such as lipids, Doxorubicin and X-rays, are clinically used in treatment of tumours. Although gold nanoparticles used in this study have not yet been approved by the regulatory agencies, their size is compatible with the requirements of renal clearance.

Cracking the code of intra-tumour heterogeneity during carcinoma response to therapy using single cell technology

George Joun[1], James Cornwell[2], Maria Parvaneh[1], Anna deFazio[3] and Naisana Seyedasli[1,4]

[1] Discipline of Life Sciences, School of Dentistry, Faculty of Medicine and Health, University of Sydney, Westmead Hospital, Westmead 2145, Australia
[2] Discipline of Bioengineering, School of Dentistry, Faculty of Medicine and Health, University of Sydney, Westmead Hospital, Westmead 2145, Australia
[3] Gynaecological Oncology Research Group, Westmead Institute for Medical Research, 176 Hawksbury Road, Westmead NSW 2145, Australia
[4] Sydney Medical School, Faculty of Medicine and Health, University of Sydney, Westmead Hospital, Westmead 2145, Australia

Background: Presence of functionally distinct subpopulations in tumours, with differential response capacities to drugs plays a central role in chemotherapy resistance/evasion. At the heart of this heterogeneity lie the so-called cancer stem cells with key roles in tumour initiation, drug resistance and metastasis.

Aims: In this study, we have analysed the molecular and cellular dynamics of heterogeneous tumour response to chemotherapy, focusing on the BMP pathway as a key player.

Methods: We have used gain and loss of function assays, state-of-the art single-cell tracking and transcriptomic technologies and novel *in-vitro* and *in-vivo* xenograft assays to address the heterogeneous dynamics of chemotherapy response in multiple lines of carcinoma cells, and in response to BMP pathway modulations.

Results: Our study highlights a slow cycling subpopulation with cancer stem cell properties in epithelial carcinoma, with the capacity to resist/evade chemotherapy. Using single cell technology, we have defined distinct signatures for this subpopulation with novel specialized capacities for DNA repair linked to specific cycling patterns. We have further demonstrated a key role for an autocrine bone morphogenic protein (BMP) signaling pathway as the master regulator of this compartment acting upstream of the slow cycling/quiescent properties, chemo-resistance and epithelial-mesenchymal transition. Further single cell tracking and transcriptome analyses confirmed that the *de novo* sensitisation to chemotherapy observed through inhibition of BMP pathway in the tumour cells and *in vivo* xenografts, majorly results from release of the slow cycling cancer stem cell compartment with adoption of active cell cycle progression patterns, and chemo-naïve gene signatures resulting in an overall more homogenous response to treatment.

Conclusions: Our findings uncover novel aspects of heterogeneous chemotherapy response in carcinoma cells supporting a key role for the BMP signaling pathway upstream of chemo-resistant carcinoma cancer stem cells. Further analysis of the molecular machinery downstream of this pathway will lead to more refined and targeted treatment strategies.

Polygenic breast cancer risk: A prospective study of uptake and outcomes among high-risk women

Tatiane Yanes[1,2], Bettina Meiser[1], Rajneesh Kaur[1], Maatje Scheepers-Joynt[3], Mary-Anne Young[4,3], Kristine Barlow-Strewart[5], Tom John[6], Yoland Antill[7], Marion Harris[8], Jo Burke[9], Tony Roscioli[10], Jane Halliday[11,12], Phillip Mitchell[2] and Paul A James[3,13]

[1] Prince of Wales Clinical School, Faculty of Medicine, UNSW Sydney, Sydney NSW, Australia
[2] School of Psychiatry, Faculty of Medicine, UNSW Sydney, Sydney NSW, Australia
[3] Parkville Familial Cancer Centre, Peter MacCallum Cancer Centre and the Royal Melbourne Hospital, Melbourne VIC, Australia
[4] Garvan Institute of Medical Research, Darlinghurst NSW, Australia
[5] Sydney Medical School Northern, University of Sydney, Sydney NSW, Australia
[6] Clinical Genetics Service, Austin Hospital, Melbourne VIC, Australia
[7] Family Cancer Clinic, Cabrini Health, Melbourne VIC, Australia
[8] Family Cancer Clinic, Monash Medical Centre, Melbourne VIC, Australia
[9] Tasmanian Clinical Genetics Service, Royal Hobart Hospital, Hobart TAS, Australia
[10] Department of Medical Genetics, Sydney Children's Hospital, Randwick NSW, Australia
[11] Public Health Genetics, Murdoch Children's Research Institute, Melbourne VIC, Australia
[12] Department of Paediatrics, University of Melbourne, Parkville VIC, Australia
[13] Sir Peter MacCallum Department of Oncology, University of Melbourne, Melbourne VIC, Australia

Background: Testing for polygenic breast cancer risk has the potential to provide personalized risk management recommendations for a significant proportion of at-risk women who receive uninformative genetic test result. Despite increasing scientific evidence regarding the utility of polygenic risk score (PRS) for families at high-risk of breast cancer, research findings are yet to be integrated into clinical practice. Before integrating polygenic information into clinical practice, it is important to understand the psychological implications.

Aim: This prospective study aims to assess uptake of breast cancer PRS and ascertain the psychosocial and behavioural implications of receiving this information.

Methods: Eligible women are invited to participate and receive their breast cancer PRS. Eligibility: affected and unaffected women currently enrolled in the Variants in Practice Study, who have a high or low PRS, and a personal and/or family history of breast cancer where genetic testing for *BRCA1/2* is negative. Participants complete three self-administered questionnaires: T1 prior to result, T2 two weeks and T3 one year post receipt of PRS.

Results: As of May 2018, 152/179 (84%) participants reported interest in receiving their PRS, with 97/152 (64%) having attended a familial cancer clinic and received their results. Only 26/179 (14%) participants have declined to receive their PRS. Logistic regression showed that uptake of PRS was associated with having daughters (OR=4.43, p=0.013), higher uncertainty avoidance (OR=0.6.30, p=<0.000) and higher response cost (OR=0.85, p=0.043). Additional preliminary analysis showed a significant reduction in perceived risk (mean difference -0.20, p=0.013), and general anxiety and depression (mean difference -1.56, p=0.002) between T1 and T2.

Conclusion: There is strong interest in receiving PRS among women at high-risk of breast cancer. Recruitment is ongoing, with additional data regarding short-term and long-term psychological and behavioural impact of receiving PRS to be collected.

A modular strategy for the bioconjugation of nanoparticles in targeted cancer theranostics

Andrew Care[1,2], Victoria Shipunova[3], Liuen Liang[2,4], Sergey Deyev[3], Andrei Zvyagin[5,6], Peter Bergquist[1,7] and Anwar Sunna[1,2]

[1] Department of Molecular Sciences, Macquarie University
[2] ARC Centre of Excellence for Nanoscale BioPhotonics (CNBP), Macquarie University
[3] Shemyakin–Ovchinnikov Institute of Bioorganic Chemistry, Russian Academy of Sciences
[4] Department of Physics and Astronomy, Macquarie University
[5] Macquarie University
[6] ARC Centre of Excellence for Nanoscale BioPhotonics
[7] Department of Molecular Medicine and Pathology, University of Auckland

Background: The coupling of nanoparticles (NPs) to cancer-targeting biomolecules (e.g. antibodies) is fundamental to their use in cancer theranostics. However, conventional bioconjugation techniques (e.g. cross-linking) often lead to the attachment of biomolecules with altered conformations and random orientations causing a reduction/loss of function. We have established a novel bioconjugation system based on a peptide (referred to as the 'Linker') that binds with nanomolar affinity to silica materials. The linker (L-) sequence can be genetically-fused to a protein of interest and the resulting recombinant fusion protein (L-Protein) binds strongly to silica.

Aim: Exploit the Linker system to build a modular platform for the bioconjugation of cancer-targeting biomolecules to silica-coated NPs, enabling applications in cancer theranostics.

Methods: The Linker was genetically-fused to either (i) Protein G (PG), which binds antibodies, or (ii) Barstar (Bs), which binds proteins tagged with its binding partner Barnase (Bn). The capacity and modularity of L-PG and L-Bs was tested by attaching various biomolecules to silica-coated NPs and then assessing their functionality.

Results: L-PG and L-Bs, mediated the orientated attachment of antibodies or Bn-tagged proteins onto silica surfaces, respectively. This bioconjugation occurred within minutes and without any complex chemical reactions. Using L-PG and L-Bs, antibodies or Bn-tagged proteins that target cancers were attached to the surface of silica-coated NPs with differing modalities (i.e. drug-doped, fluorescent dye-doped, lanthanide-doped upconversion, and superparamagnetic). These functionalised NPs were successfully applied in the targeted imaging and/or therapy (e.g. photodynamic therapy) of various cancer cell types, including brain, breast, colorectal, and bladder cancers. Additionally, this bioconjugation technology was shown to be stable and functional in complex biological fluids such as mouse whole blood.

Conclusion: This versatile bioconjugation platform for silica-coated NPs has the potential to be translated into clinical applications, including medical diagnostics (e.g. point-of-care testing) and targeted cancer therapies (e.g. drug delivery).

Prevention of ADT adverse effects using a 6-month home-based progressive resistance training program

Teresa Lam[1,2,3], Birinder Cheema[4], Amy Hayden[5,6], Howard Gurney[7], Shivanjini Gounden[4], Navneeta Reddy[3], Glenn Stone[8], Mark McLean[3] and Vita Birzniece[1,3,9]

[1] School of Medicine, Western Sydney University, Penrith, NSW, Australia
[2] Department of Diabetes and Endocrinology, Westmead Hospital, Westmead, NSW, Australia
[3] Department of Diabetes and Endocrinology, Blacktown Hospital, Blacktown, NSW, Australia
[4] School of Science and Health, Western Sydney University, Penrith, NSW, Australia
[5] Department of Radiation Oncology, Blacktown Hospital, Blacktown, NSW, Australia
[6] Department of Radiation Oncology, Westmead Hospital, Westmead, NSW, Australia
[7] Department of Medical Oncology, Westmead Hospital, Westmead, NSW, Australia
[8] School of Computing, Engineering and Mathematics, Western Sydney University, Penrith, NSW, Australia
[9] Garvan Institute of Medical Research, Sydney, NSW, Australia

Introduction: Androgen deprivation therapy (ADT) is a common treatment for men with prostate cancer, but it may result in adverse effects on body composition, insulin resistance and quality of life (QOL). Exercise interventions, including progressive resistance training (PRT), may ameliorate many of these adverse effects. However, existing studies have been aimed at reversing established ADT-induced metabolic changes utilizing heavily supervised exercise programs, which are difficult to implement in routine clinical practice. We investigated whether a home-based PRT program, instituted at the start of ADT, could prevent adverse effects over a 6-month period.

Patients and Methods: Twenty-five patients with prostate cancer were randomly assigned to either usual care (UC) (n = 12) or PRT (n = 13) (3 sets of 8-9 exercises targeting all major muscle groups using 8-12 repetition maximal loads) starting immediately after their first ADT injection. Body composition, body cell mass (BCM; a functional component of lean body mass), insulin sensitivity, QOL and muscle function were measured at baseline, 6 weeks and 6 months. Data were analyzed by linear mixed model.

Results: At 6-months, patients randomised to PRT preserved BCM compared to UC (-0.4□1.6kg vs -2.0□1.1kg; $p<0.05$). There were no significance differences between groups regarding changes in fat mass (1.3±2.0kg vs 2.7□1.6kg; $p=0.10$). Insulin sensitivity, as measured by the Matsuda Index (MI), increased at 6 weeks in PRT patients compared to a decline with UC (2.3□2.7 vs -0.3□1.6; $p<0.01$). This between-group difference in MI was not maintained at 6 months. QOL significantly improved in patients receiving PRT at 6 months compared to UC, particularly in the mental health (3.6±5.2 vs -2.6□6.2; $p<0.01$) and pain domains (8.3□14.2 vs -10.0□11.6; $p<0.01$).

Conclusion: A home based PRT program initiated at the start of ADT exerts significant benefits over UC in maintaining muscle mass, glucose metabolism, and QOL.

TMEM and Menacalc: new prognostic markers for breast cancer

Thomas Rohan[1], Maja Oktay[2], Joseph Sparano[3], Joan Jones[2], David Entenberg[2] and John Condeelis[2]

[1] Dept. of Epidemiology and Population Health, Albert Einstein College of Medicine
[2] Albert Einstein College of Medicine
[3] Montefiore Medical Center

Breast cancer mortality results largely from systemic, hematogenously-disseminated metastatic disease. To decrease metastatic risk, many breast cancer patients are treated with adjuvant chemotherapy, often unnecessarily. Several gene expression assays (e.g., Oncotype DX®, MammaPrint®™) provide more accurate prognostic information than classical clinicopathologic features. However, they each provide similar prognostic information driven largely by proliferation-/estrogen-regulated genes and not by the intrinsic propensity of a tumor to metastasize or interact with its microenvironment. We review here two new mechanism-based markers of metastatic risk: TMEM and $Mena^{calc}$.

Using multiphoton intravital imaging of mice with mammary tumors, we have observed that tumor cells migrate toward blood vessels accompanied by macrophages and intravasate exclusively at microanatomic sites called TMEM (Tumor Microenvironment of Metastasis), composed of a complex containing a Mena-expressing tumor cell, a pro-angiogenic macrophage, and a vascular endothelial cell, in direct contact. Gene expression profiling of migrating TMEM-associated cancer cells has led to identification of signaling pathways activated in migrating and intravasating tumor cells. These pathways involve differential expression of Mena isoforms. Mena undergoes alternative splicing resulting in multiple mRNAs that encode functionally distinct protein isoforms expressed in specific tissues and cell-types. The Mena expression pattern $Mena^{ClassicHi}$/ $Mena^{INVHi}$/$Mena11a^{Lo}$ (scored as the fluorescent intensity of antibody staining of (pan-Mena - Mena 11a = $Mena^{calc}$)) is involved in breast tumor cells undergoing TMEM-mediated dissemination *in vivo*. Investigation of the association between TMEM and specific Mena isoforms by overexpressing either $Mena^{INV}$ or Mena11a in tumor cells and observing their phenotypes by imaging in vivo has shown that $Mena^{INVHi}$-expressing tumor cells greatly enhance tumor cell migration and TMEM-mediated intravasation, while Mena11a-expressing cells suppress these phenotypes. Consistent with these findings in mice, in human breast tumors, TMEM and $Mena^{calc}$ scores are individually prognostic for metastasis in ER^{+}/HER2- patients and add complementary information to prognostic assays that are based on proliferation.

Skp2-mediated stabilization of MTH1 protects melanoma cells from oxidative stress

Lei Jin[1], Jia Yu Wang[1], Guang Zhi Liu[2], James S. Wilmott[3], Ting La[1], Yu Chen Feng[1], Hamed Yari[1], Xu Guang Yan[1], Rick F. Thorne[1], Richard A. Scolyer[3] and Xu Dong Zhang[1]

[1] The University of Newcastle
[2] Henan Provincial People's Hospital
[3] The University of Sydney

Background: Cancer cells often contain elevated levels of reactive oxygen species (ROS) resulting from oncogenic stimulation. On one hand, ROS promote cancer cell survival, proliferation and metastasis. On the other, high levels of ROS suppress tumor growth via causing DNA damage. One mechanism that protects cancer cells from high levels of ROS is the expression of MutT homolog 1(MTH1), which sanitizes oxidized dNTP pools through converting 8-oxo-dGTP and 2-OH-dATP into monophosphates, thus preventing their incorporation into genomic DNA. We have recently found that melanoma cells are sensitive to the MTH1 inhibitor TH588-induced killing and MTH1 silencing enhances melanoma cell death triggered by the oxidative stress inducer elesclomol, indicating that MTH1 is important for melanoma survival. However, how MTH1 expression is regulated in cancer cells is still largely unknown.

Aim: To identify mechanisms that protect melanoma cells from ROS-induced DNA damage via regulating MTH1 expression.

Methods: Mass Spectrometry, Ubiquitination analysis, Immunoprecipitation, Immunohistochemistry, Immunofluorescence, Western Blotting, qPCR

Results: MTH1 is regulated by polyubiquitination mediated by the E3 ligase Skp2. In melanoma cells, MTH1 was upregulated mainly due to its improved stability caused by K63-linked polyubiquitination. While Skp2 along with other components of the Skp1-cullin-F-box (SCF) ubiquitin ligase complex were physically associated with MTH1, blocking the SCF function ablated MTH1 ubiquitination and expression. Conversely, overexpressing Skp2 elevated MTH1 levels associated with an increase in its K63-linked ubiquitination. In melanoma cell lines and patient specimens, we observed a positive correlation of Skp2 and MTH1 expression. Mechanistic investigations showed that Skp2 limited DNA damage and apoptosis triggered by oxidative stress and that MAPK upregulated Skp2 and MTH1 to render cells more resistant to such stress.

Conclusions: Collectively, our findings identify Skp2-mediated K63-linked polyubiquitination as a critical mechanism responsible for MTH1 upregulation in melanoma, with potential implications to target the MAPK/Skp2/MTH1 pathway to improve its treatment.

Dietary sucrose intake increases liver tumour burden in a mouse model of diethylnitrosamine-induced liver cancer

Ghazal Alipour[1], Mahmoud Karimi Azar[1], Vikki Ho[1], Mehdi Ramezani Moghadam[1], Saeed Esmaili[1] and Jacob George[2]

[1] Storr Liver Centre, Westmead Institute for Medical Research, University of Sydney at Westmead Hospital
[2] Westmead Institute for Medical Research, University of Sydney and Westmead Hospital

Background and aim: Globally, hepatocellular carcinoma (HCC) ranks as the 6th most common cancer and the second leading cause of cancer related death. HCC in NSW is the fastest growing solid organ tumour. A large body of evidence shows that nutrition plays a key role in cancer development. Type 2 diabetes and dietary intake of sugar are also suggested to be associated with multiple types of cancers. Currently, there is an unmet need for studies to determine how dietary factors possibly affect HCC development.

Methods: We studied both the short and long term effects of a sucrose rich diet on liver tumour development in diethylnitrosamine (DEN)-treated mice. Male C57BL6 wild type mice were fed the sucrose rich diet or standard chow for 14 (short term) or 26 weeks (long term study). The liver pathology and tumour burden, glucose tolerance and serum lipids, as well as the liver and spleen immune responses were profiled.

Results and Conclusions: Tumour multiplicity and size were enhanced by short term sucrose rich diet feeding (ns). This diet for 14 weeks did not affect mouse blood glucose or lipids. Long term sucrose rich diet feeding induced obesity and liver steatosis, and elevated serum triglyceride while impairing glucose tolerance. These mice exhibited a 3-fold increase in liver tumour numbers ($P<0.0001$) and a 10-fold increase in tumour size ($P<0.01$) compared to chow fed mice. We conclude that long term excessive dietary sucrose consumption enhances liver tumour development. Since nutrition is a modifiable environmental risk factor, our data highlights the importance of nutrition modification as a potential strategy to reduce HCC risk.

Public perceptions of thyroid cancer overdiagnosis, overtreatment and communication strategies: a qualitative study

Caitlin Semsarian[1], Brooke Nickel[1], Ray Moynihan[1,2], Alex Barratt[1], Juan P Brito[1,3], Don McLeod[4], Susan Jordan[4,5], Darlene Cox[6] and Kirsten McCaffery[1]

[1] Wiser Healthcare, School of Public Health, University of Sydney
[2] Centre for Research in Evidence-Based Practice, Bond University
[3] Division of Endocrinology, Diabetes, Metabolism and Nutrition, Mayo Clinic
[4] QIMR Berghofer Medical Research Institute
[5] School of Public Health, The University of Queensland
[6] Health Care Consumers Association

Background: Advancing diagnostic technologies and widespread access to healthcare services have led to an increase in the detection of low-risk thyroid cancers worldwide. One strategy proposed by international experts to reduce the harms of overdiagnosis and overtreatment is to change the terminology used to describe low-risk cancers. Replacing the term 'cancer' may help alleviate patient anxiety and encourage appropriate treatment. It is crucial to investigate community perceptions of this strategy to ensure that clinical communication is consistent with community understanding and preferences.

Aim: To investigate public perceptions of overdiagnosis and overtreatment in low-risk thyroid cancer and explore opinions regarding the proposed strategy to change the terminology of low-risk cancers.

Methods: Qualitative study using focus groups (n=47 participants) that included a guided group discussion and presentation explaining thyroid cancer, overdiagnosis and overtreatment, and proposed communication strategies. Transcripts were analysed thematically.

Results: Participants expressed concern regarding overdiagnosis and overtreatment of thyroid cancer. However, participants remained divided over the strategy to change the terminology. The dominant argument supporting the strategy was that changing the terminology would reduce the negative psychological impact and stigma associated with the term 'cancer'. Participants against the proposed strategy were concerned about the risk of cancer progression and articulated that changing the terminology may create confusion, or cause patients to treat surveillance and other management procedures as less urgent. Despite varied views towards the proposed strategy, all participants strongly favoured further patient and public education.

Conclusion: Similar to the medical community, the public is uncertain about whether changing the terminology of low-risk thyroid cancer (and other low-risk conditions) is an adequate strategy to reduce overdiagnosis and overtreatment. However, there is a strong desire for greater patient and public education of these issues and this should be addressed.

Australia's pilot trial of digital breast tomosynthesis (3Dmammography) population-based screening: Interim results

Nehmat Houssami[1], Darren Lockie[2], Michelle Clemson[2], Vicki Pridmore[3] and Petra Macaskill[4]

[1] University Of Sydney
[2] Maroondah BreastScreen
[3] BreastScreen Victoria
[4] University of Sydney

Background: International studies show that integrating digital breast tomosynthesis (pseudo 3D-mammography) in screening improves detection compared to conventional (2D) mammography. At present, tomosynthesis is not endorsed for primary screening in Australia's population-based screening program (BreastScreen).

Aim: To conduct a *pilot* of tomosynthesis screening, to assess the feasibility of using tomosynthesis for screening and to estimate screen-detection measures in service screening in BreastScreen.

Methods: A prospective trial embedded in BreastScreen Victoria (Maroondah BreastScreen; ACTRN12617000947303) commenced in August 2017 and is half-way to the accrual target of 5,000 women who will receive tomosynthesis (with synthesized 2D-mammograms) screening. Service preparedness included modifying the information/consent package provided to women (including 'opt-out' option), as well as training for administrative and imaging staff. Pre-planned interim analysis of the trial's secondary outcomes is interpreted relative to a concurrent cohort of mammography-screened women from the same timeframe and population.

Results: From all screening participants, 7.0% opted out of the trial, 2026 participants (median age 57 (IQR 52-64) years) had tomosynthesis screening, and 2036 had standard mammography screening. Recall to assessment based on a positive screen was 5.1% for tomosynthesis and 3.1% for mammography ($p<0.05$). Mean [median] screen-reading time for tomosynthesis (157 [70] seconds) was 3-4 times that of mammography (53 [16] seconds). Mean [median] glandular dose per view for tomosynthesis (2.5 [2.5] mGy) was roughly twice that of mammography (1.3 [1.24] mGy).

Conclusion: Initial implementation of tomosynthesis screening in a BreastScreen service was feasible and was also acceptable to women, however, tomosynthesis increased recall and screen-reading time relative to standard mammography screening. The increased radiation burden requires further exploration and monitoring. These findings will be considered alongside cancer detection rates at completion of the trial. Our work highlights the relevance of local evaluation in cancer screening programs to inform further research and potential translation into screening policy.

Germline genomic analysis in childhood cancer patients suspected of genetic predisposition to cancer

Dianne E Sylvester[1], Yuyan Chen[1], Robyn Jamieson[2], Luciano Dalla-Pozza[3] and Jennifer A Byrne[1]

[1] Kids Research, Children's Hospital at Westmead
[2] Childrens Medical Research Institute, Westmead
[3] Cancer Centre for Children, Children's Hospital at Westmead

Background: Genetic investigation of childhood cancer patients suspected of cancer predisposition has previously been restricted by resource availability. With advancing technologies, coupled with decreasing costs, it is now feasible to detect gene variants in patients through genomic analysis of germline DNA. This approach could extend benefits to cancer patients and families through the possibility of improved therapy, prognosis and/or surveillance.

Aim: This study aims to expand existing knowledge of cancer predisposing germline variants in childhood cancer patients with a phenotype indicative of a genetic susceptibility to cancer, through the application of genomics.

Methods: We utilised whole exome sequencing to analyse germline DNA from retrospectively- (n=70) and prospectively- (n=6) identified childhood cancer patients at the Cancer Centre for Children, who were diagnosed with multiple cancers and/or family history of cancer and/or diagnosis or family history of a genetic disorder. Sequencing data were filtered for rare non-synonymous exonic variants and copy number variants in genes associated with cancer predisposition, DNA repair and/or somatic variation in cancer (n=1047 genes).

Results: We found that 17/76 (22.4%) childhood cancer patients carried pathogenic or likely pathogenic germline variant(s) in 11 genes known to predispose to cancer. The genotype-phenotype relationship could be anticipated in 8/17 (47%) cases, with the remaining 9 (53%) cases carrying variants affecting genes associated with adult-onset cancers, or recessive disease.

Conclusion: In childhood cancer patients with a phenotype indicative of a genetic susceptibility to cancer, we detected likely predisposing germline variants in known cancer predisposition genes in 17/76 (approximately 1 in 5) patients. However, no clear association between the genetic diagnosis and patient phenotype was found in close to half (9/17) of these patients. Integration of germline genomic analyses into the paediatric oncology clinic requires an improved understanding of the significance of gene variants associated with adult-onset cancers in childhood cancer patients.

Understanding Fibroblast Activation Protein as a Molecular Target in Tumour Stroma Using Degradomics and Proteomics

Hui Emma Zhang[1], Elizabeth Hamson[1], Sumaiya Chowdhury[1], Maria Magdalena Koczorowska[2], Stefan Tholen[3], Charles Bailey[1], Xin Wang[4], Angelina Lay[1], Stephen Twigg[5], Ben Roediger[1], Martin Biniossek[2], Geoffrey McCaughan[1], Fiona Keane[1], Oliver Schilling[2], William Bachovchin[6] and Mark Gorrell[1]

[1] Centenary Institute
[2] University of Freiburg
[3] Stanford University
[4] Westmead Millennium Institute
[5] Charles Perkins Centre, University of Sydney
[6] Tufts University

Background: Liver cancer is the 2nd most common cause of cancer death and cancer risk increases in fatty liver, fibrosis and cirrhosis. The protease fibroblast activation protein-alpha (FAP) has a unique post-proline cleaving activity. FAP is highly upregulated in fibroblasts and pericytes in tumours.

Aim: To understand of the roles of FAP in the pathogenesis of liver cancer and to identify novel targets for therapy.

Methods: Proteomics and degradomics with FAPgko (gene knockout) fibroblasts were performed to identify substrates of FAP. Animal models of diet induced obesity, liver fibrosis and skin wound healing were performed.

Results: *In vitro,* using proteomics and degradomics, we discovered novel natural substrates of FAP that have roles in extracellular matrix (ECM) by directly cleaving collagens and many other ECM proteins, as well as by indirectly altering the abundance of several ECM-degrading proteases and their inhibitors. Other substrates identified pointed to the role of FAP in metabolism, coagulation and immunoregulation. *In vivo*, we found that FAP drives fatty liver disease and liver fibrosis, which greatly increase the risk of developing liver cancer. The FAPgko mouse, and our unique FAPgki (gene knock-in) mouse that lacks only the enzyme activity of FAP, in a model of diet induced obesity, have less insulin resistance, steatosis, glucose intolerance and hepatocyte damage. Both FAP gko and gki mice in a model of chemical induced liver fibrosis have less fibrosis. In a model of skin wound healing, FAP gko mice had delayed wound closure and less collagen in the healed wounds.

Conclusion: These data expand the understanding of FAP in chronic liver diseases and cancer, where it may regulate metabolism, ECM remodeling, and immune response. The outcome will lead to the foundation of a novel therapy to treat liver cancer, which would have direct clinical translation.

CADg: a novel mammographic computer-aided detection tool incorporating the gist of the abnormal

Ziba Gandomkar[1], Ernest Ekpo[1], Sarah Lewis[2], Kriscia Tapia[1] and Patrick Brennan[2]

[1] University of Sydney
[2] The University of Sydney, Australia

Background: Expert radiologists' first impression of the normality or abnormality of a mammograms is highly associated with whether a mammogram contains a malignancy. This impression is based on global properties or "gist signal", rather than local image characteristics. However, the signal could be overruled during subsequent visual search.

Aim: To propose CADg, a CAD tool for mammography based on global image features.

Materials and Methods: To record the gist responses, 23 radiologists and breast physicians provided an abnormality score on a scale from 0 (confident normal) to 100 (confident abnormal) to 80 unilateral CC mammograms based on a half-second flashing of the image. Forty mammograms contained a biopsy-proven cancer while the rest were confirmed to be cancer-free based on at least 2 years of follow-up. Holistic computer-extracted features were also calculated from each mammogram to complement global image statistics described by the gist. The features and the gist response were fed into an ensemble of decision trees. Sequential forward feature selection and leave-one-out cross-validation were used. As a baseline, each case was independently assessed by a separate sample of at least 40 radiologists using the usual presentation and reporting mechanisms.

Results: From cancer-containing mammograms, 15, 24, and 30 lesions were missed by at least 50%, 40%, 30% of readers following the usual reporting process. Using CADg, trained for each individual radiologists, the corresponding numbers were 3, 7, 11 lesions. With regard to the cancer-free images, the numbers of normal cases reported as abnormal at least by 30% of readers with usual reporting and gist presentation were 20 and 9, respectively. When the gist responses were averaged across all readers and fed into CADg, it achieved an Area under Receiver Operating Characteristics curve of 0.96.

Conclusions: The global image properties and statistics have the potential to improve the performance of current CADs, which mainly rely on the localized analysis of mammograms to identify suspicious areas.

A systematic review of available body image measures for head and neck cancer (HNC)

Chindhu Shunmuga sundaram[1], Claudia Rutherford[1], Phyllis Butow[1], Puma Sundaresan[1] and Haryana Dhillon[1]

[1] University of Sydney

Aims: Globally HNC is common and estimated to cause three million deaths annually. Patients with HNC undergo a challenging journey both physically and emotionally. Owing to its visibility, HNC treatment results in psychosocial problems, disfigurement and dysfunction. Changes to physical appearance are a major stressor, affecting self-esteem, physical, social, and role functioning, impacting health-related quality of life (HRQoL). This review aimed to: 1) identify HNC-specific patient reported outcome measures (PROMs) used to assess body image; 2) assess these PROMs' conceptual coverage; 3) appraise PROMs' development process and psychometric properties; and 4) determine the most appropriate body image PROM(s) to use in HNC setting.

Methods: Five online databases were searched (July 2007-July 2017) for studies (English language) done on body image in patients with HNC diagnosis. Studies were screened for eligibility by one reviewer (10% by a second reviewer). Searches were limited to papers published in the past 10 years to reflect advances in cancer treatments. From the available body image frameworks, we compiled a conceptual schema consisting of eighteen clinically relevant body image issues important in HNC setting. Risk of bias was assessed regarding PRO assessment in the studies. Selected measures were appraised for psychometric characteristics and content.

Results: A total of 245 records were identified. Eighteen quantitative studies with PRO met our inclusion criteria reporting eight PROMs. In addition to this, the reviewer searched three PROM databases, identified 62 measures, removed duplicates, and screened for inclusion criteria. Five measures were short-listed and appraised in this review for psychometric properties. Derriford Appearance Scale (DAS) 59, DAS 24, and Body image scale (BIS) cover (>55%) the body image conceptual schema, were developed based on literature, patient interviews and clinician opinions, and have evidence of internal consistency (Cronbach alpha >0.7), validity and responsiveness to change.

Conclusion: Three body image PROMs with adequate coverage of HNC issues to be used in research and clinical practice were identified. Our conceptual schema provides the basis for selecting clinically relevant body image issues in HNC setting.

Dipeptidyl peptidase inhibition in experimental hepatocellular carcinoma

James Henderson[1,2], Jinbiao Chen[1], Wengen Wu[3], Jack Lai[3], Geoffrey McCaughan[1,2,4], William Bachovchin[3], Hui Emma Zhang[1,2] and Mark Gorrell[1,2]

[1] Centenary Institute
[2] University of Sydney
[3] Tufts University
[4] Royal Prince Alfred Hospital

Background: Hepatocellular carcinoma (HCC) is the 2nd leading cause of cancer mortality. Novel medical therapies are needed. Dipeptidyl peptidases (DPPs) are abundant in liver and in tumours and might be a suitable therapeutic target. IO-4175 is a prototype multi-DPP inhibitor showing promise in a lung cancer model. Mechanisms of action are believed to include inflammasome activation that stimulates immunity as well as protecting chemokines from degradation.

Aim: To evaluate IO-4175 as a therapy for primary HCC in mice.

Methods: To generate HCC, male mice received diethylnitrosamine (DEN) once, and then atherogenic high fat diet and thioacetamide from weaning. IO-4175 (6 mg/kg) or vehicle control were administered at 12-20 weeks of age. Inflammation, steatosis and fibrosis were measured by histopathology. Data is presented as mean and standard deviation (SD) and p value from non-parametric statistic.

Results: IO-4175 treatment decreased hepatic DPP4 and DPP8/9 enzymatic activity, showing that IO-4175 inhibited the targeted enzymes. IO-4175 treated mice had fewer macroscopic liver spots (6.8, SD 5.4 vs 12.8, SD 7.4; p=0.04), and trended toward significance of fewer HCC (0.5, SD 1.4 vs 1.3, SD 1.4) and fewer high grade dysplastic lesions (1.25, SD 1.5 vs 1.7, SD 2.06) per section. The IO-4175 treated livers had increased inflammation (2, SD 0.8 vs 0.7, SD 0.7; p=0.005) and fibrosis (3.1, SD 0.8 vs 1.9, SD 0.8; p=0.01) scores compared to vehicle control.

These data are consistent with an immunotherapeutic mode of action that attracts leukocytes into lesions. Immunotherapy in humans has been applied successfully to advanced HCC, in which a pro-fibrotic consequence of attracting leucocytes that include anti-tumour cytotoxic lymphocytes may be tolerated when causing tumour regression.

Conclusion: A prototypic multi-DPP inhibitor showed promise for anti-tumour benefit and immunostimulation in our novel HCC model. DPP - targeted compounds may become a novel immunotherapy in HCC.

Shock and ROR: Targeting ROR1 & ROR2 in a pre-clinical patient derived model of ovarian cancer.

Claire Henry[1], Estelle Llamosas[2], Neville Hacker[3] and Caroline Ford[1]

[1] Gynaecological Cancer Research Group, Lowy Cancer Research Centre, Faculty of Medicine, University of New South Wales, Australia.
[2] UNSW Sydney
[3] Gynaecological Cancer Centre, Royal Hospital for Women, Sydney, Australia

BACKGROUND: New targets for ovarian cancer treatment are critically needed. The Wnt receptors ROR1 and ROR2 are overexpressed in all histotypes of ovarian cancer and appear to play a role in both the tumour and stromal compartments. *In vitro* studies support the role of these receptors in ovarian cancer migration and invasion. However, these previous studies have utilised simple 2D *in vitro* models to investigate cancer cell growth and migration, which does not allow investigation of stromal involvement in ROR driven metastasis.

AIM: To investigate targeting ROR1 and ROR2 in a primary co-culture 3D model of epithelial ovarian cancer dissemination to the omentum.

METHODS: Primary fibroblasts (NOF) and mesothelial (HPMC) cells were isolated from fresh samples of omentum collected from women with benign or non-metastatic conditions and cultured with collagen to produce a organotypic 3D model. Stable shRNA knockdown of ROR1, ROR2 and double ROR1/ROR2 in OVCAR4 cells were incorporated into the 3D model to measure adhesion, or using a transwell to measure invasion. Gene expression changes in primary cells upon OVCAR4 interaction was evaluated using indirect transwell co-culture.

RESULTS: Double knockdown of ROR1 and ROR2 strongly inhibited cell adhesion ($p<0.05$) and invasion ($P<0.05$) to the omentum model. ROR2 was up regulated in primary fibroblasts when cultured with OVCAR4 ($P=0.05$) and ectopic overexpression of ROR2 in NOFs inhibited cell proliferation ($P<0.01$) but increased cell migration**.**

CONCLUSION: The combination of ROR1 and ROR2 signalling influences ovarian cancer dissemination to the omentum, however ROR2 may also play a role in stromal activation during metastasis. Therefore, targeting both ROR1 and ROR2 may be a powerful approach to treating ovarian cancer. The development of a number of monoclonal antibodies targeting ROR1 currently in phase 1 trials for other tumour types makes this clinically feasible in the future.

ROR1 and ROR2 play distinct and opposing roles in endometrial cancer.

Claire Henry[1], Estelle Llamosas[1], Benjamin Daniels[1], Amy Coopes[1], Katrina Tang[2] and Caroline Ford[1]

[1] UNSW Sydney
[2] South Eastern Area Laboratory Services Pathology, Prince of Wales Hospital

BACKGROUND: In recent years, the Wnt signalling pathway and the ROR1 and ROR2 receptors have been implicated in a range of cancers. These receptors have been described as prospective therapeutic targets, and we have previously shown their importance in ovarian cancer metastasis.

AIMS: This study investigated the role of ROR1 and ROR2 in endometrial cancer.

METHODS: Immunohistochemistry for ROR1 and ROR2 was performed in a patient cohort, and expression was correlated with clinicopathological parameters including type, stage, grade, myometrial invasion, lymphovascular involvement, patient age and survival. The functional role of these receptors in endometrial cancer was investigated via siRNA knockdown of ROR1 and ROR2 in three cell line models (KLE, RL95-2 and MFE-319). Effects on proliferation, adhesion, migration and invasion were measured.

RESULTS: High ROR1 expression in patient samples correlated with worse overall survival ($p=0.0169$) whilst high ROR2 expression correlated with better overall survival ($p=0.06$). ROR1 knockdown in KLE cells significantly decreased proliferation ($p=0.047$) and reduced migration and invasion. ROR2 knockdown in RL95-2 cells increased cell migration and invasion ($p=0.011$). Double ROR1 and ROR2 knockdown in MFE-319 cells decreased adhesion and significantly increased cell migration ($P=0.008$) and invasion ($p<0.001$).

CONCLUSION: ROR1 and ROR2 play distinct roles in endometrial cancer. ROR1 may promote tumour progression, similar to its role in ovarian cancer, while ROR2 may act as a tumour suppressor in endometrioid endometrial cancer, similar to its role in colorectal cancer. With several ROR-targeting therapies currently in development and phase I clinical trials for other tumour types, this study supports the potential of these receptors as therapeutic targets for women with endometrial cancer.

Transient 'priming' by FAK inhibition improves sensitivity to standard-of-care in Pancreatic Ductal Adenocarcinoma

Kendelle Murphy[1], Claire Vennin[1], Morghan Lucas[1], James Conway[1], Sean Warren[1], Joanna Skhinas[1], Astrid Mangneau[1], Thomas Cox[1], Max Nobis[1], Yingxiao Wang[2], Jennifer Morton[3], Owen Sansom[3], Marina Pajic[1], David Herrmann[4] and Paul Timpson[4]

[1] Garvan Institute of Medical Research & The Kinghorn Cancer Centre, Cancer Division, Sydney, NSW 2010, Australia
[2] Department of Bioengineering, University of Illinois, Urbana-Champaign, Illinois, USA
[3] Cancer Research UK, Beatson Institute, Glasgow, UK
[4] Garvan Institute of Medical Research

Background: The extensive stromal desmoplasmia, characteristic of pancreatic ductal adenocarcinoma (PDAC) alters mechanical tumour-stroma integrations, promoting tumour development and metastatic spread. Current chemotherapy remains generally ineffective meaning that PDAC is predicted to be the second leading cause of cancer mortality by 2030. In highly metastatic mouse models of PDAC, we observed enhanced extracellular matrix (ECM) deposition and remodelling throughout disease progression, which occurred in parallel with increased Focal Adhesion Kinase (FAK) expression and activity.

Aim: Consequently, we aim to fine-tune FAK inhibition of both the tumour and stroma to improve overall response to chemotherapy.

Methods: Intravital imaging of the FUCCI cell cycle reporter and a Förster Resonance Energy Transfer biosensor for FAK activity, in parallel with Second Harmonic Generation imaging of collagen, were used to dynamically monitor tumour cell response to standard-of-care therapy, gemcitabine/Abraxane, FAK inhibition and ECM organisation respectively. Complementing *in vivo* metastatic studies, we used 3D *in vitro* models of invasion, anchorage-independent growth and shear-stress to assess the response of primary PDAC and patient-derived cell lines to treatment.

Results: Intravital imaging was used to systematically demonstrate that FAK inhibition modulates the ECM prior to standard-of-care therapy, enhancing treatment efficacy whilst reducing metastatic spread *in vivo*. Further analysis revealed that FAK inhibition sensitised cells to shear stress, impairing metastatic colonisation and the establishment of fibrotic niches in the liver. Stratified patient samples suggest a subset of patients with high FAK activity are likely to respond to FAK priming regimes, where fine-tuned ECM manipulation prior to chemotherapy may improve patient outcome.

Conclusion: This subtype-specific fine-tuned stromal manipulation may allow us to maximise gemcitabine/Abraxane therapy whilst reducing drug toxicity and potentially reducing metastatic spread in patients.

Translational Significance: Using stratified patient-derived models we reveal a potential for tailored and short-term stromal manipulation on a personalised level.

Workforce Participation of Australian Women with Breast Cancer

Joanne Lewis[1], Lynette Mackenzie[1] and Deborah Black[1]

[1] University of Sydney

Background: Women with breast cancer have reported returning to employment as a significant milestone in their survivorship journey. Apart from the financial benefit of returning to work after breast cancer, women also highlight the psychological and social benefits of returning to 'normality'. International research suggests that 20-30% of women do not return to work after breast cancer, with limited evidence from Australian research.

Aim: To identify workforce participation patterns for women with breast cancer over a 17 year period and investigate associations between diagnosis and employment status.

Method: Using the 1946-1951 birth cohort of the Australian Longitudinal Study on Women's Health, latent class analysis was used to identify workforce participation patterns among women that were diagnosed with breast cancer. Multinomial logistic regression was used to examine associations between work patterns and breast cancer, while adjusting for other factors.

Results: Five latent classes were identified. Overall, healthy women were more likely to be in 'at work' classes, whilst women with breast cancer were more likely to be in the 'not at work' class. 448 women diagnosed with breast cancer between 1998 and 2010 provided pre and post breast cancer diagnosis work status. For full time workers with breast cancer, 48% were able to return to their full time employment three years after diagnosis. But 52% only returned to part time work or were not in paid work at all.

Conclusion: These results reveal the extent to which a breast cancer diagnosis impacts on employment participation rates for women. Occupational therapists understand the importance of productive occupations in client's lives. There are opportunities for occupational therapists to build partnerships across health, employment and insurance sectors and to consider different service delivery models to support women with returning to work as part of their cancer survivorship journey.

Heterogeneity in the single-cell signalling response promotes chemoresistance in neuroblastoma

David Croucher[1]

[1] Garvan Institute of Medical Research

Background: High-risk neuroblastoma is an aggressive, childhood tumour with no clinically successful targeted therapies and high rates of chemoresistance. Approximately 15% of patients do not respond to treatment with chemotherapy, and a further 40-50% of patients will relapse following an initial response.

The emergence of chemoresistance is therefore a major clinical problem for neuroblastoma, and indeed most tumour types where chemotherapy remains the frontline treatment. A number of theories have been proposed to describe the dynamics of drug response and the expansion of resistant cell clones, which usually invoke the prior existence of a resistant stem cell population, a low frequency somatic mutation or the *de novo* acquisition of new mutations.

Aim: In contrast to these predominantly genetic mechanisms, we now seek to demonstrate that the survival and propagation of a single cell clone can arise merely through the inherently noisy process of gene expression and the non-linear behaviour of signalling pathways.

Methods: We have previously demonstrated that *in silico* patient-specific modelling of apoptotic signalling can stratify neuroblastoma patient cohorts and provide robust biomarkers of patient survival. Using kinase activity biosensors and high-throughput imaging we now aim to apply this model to single-cell populations and identify low frequency chemoresistant cells.

Results: We now demonstrate that a small percentage of neuroblastoma cells cannot activate a sufficient drug-induced signalling response to reach an in-built apoptotic threshold. Furthermore, we also apply rationalised therapeutic strategies aimed at lowering this apoptotic threshold and demonstrate that this significantly increases the efficacy of standard-of-care neuroblastoma chemotherapy drugs in both the primary treatment and relapse settings.

Conclusion: Through a combination of mathematical modelling and single cell imaging we have demonstrated a novel mechanism of stochastic single-cell chemoresistance. We can now leverage this detailed mechanistic data to prevent the emergence of chemoresistance and improve outcomes for high-risk neuroblastoma patients.

A new strategy to reduce prostate cancer stem cells by combining of BBI and α-TOS

Saki Kaneko[1], Takumi Yamazaki[2], Kazunori Kato[3] and Tomohiro Yano[1]

[1] Graduate School of Food and Nutritional Sciences, Toyo University
[2] Department of BioMedical Engineering, Toyo University
[3] Department of Biomedical Engineering, Toyo University.

Background: Cancer stem cells (CSCs) contribute to oncogenesis and recurrent cancer. However, there is still no definite effective prevention and treatment strategy against cancer stem cells. Soybean is known as a cancer-preventive food. The most predominant protease inhibitor in soybeans is Bowman-Birk inhibitor (BBI), a well-established cancer chemo-preventive agent. Our previous study has shown that BBI induces connexin43 (Cx43), a tumor suppressor gene for prostate cancer that forms the gap junction (GJ). The formation of GJ can restore normal cell functions. This study was preformed to reduce CSCs characteristics through the induction of Cx43. On the other hand, it is known that mitocan has strong cancer suppression effect by targeting mitochondria, so we focused on Alpha-Tocopherol succinate (α-TOS) as a mitocan.

Aim: Our aim is to propose a new preventive strategy targeting on prostate cancer stem cells by combining BBI and TOS.

Method: Androgen-dependent prostate cancer cells and LNCaP were used, and we created spheroid-formed CSCs from LNCaP parental cells. We evaluated cell viability using WST-1 assay, the mRNA level through RT-Real time PCR, the protein level using Western blotting, and the localization of protein through Immunohistochemistry.

Result: Level of Cx43 mRNA and protein were increased by BBI. In parallel with the Cx43 induction, cell viability was inhibited in a dose-dependent manner, and some markers of CSCs and chemo-resistance was decreased. The combination of BBI and TOS could suppress the cell survival at low concentrations of TOS. Furthermore, mRNA expression of anti-apoptotic protein Bcl-xl was suppressed.

Conclusion: Herein, we propose a new strategy targeting prostate cancer stem cells. BBI induces the differentiation and decreases the characteristics of cancer stem cells. Subsequently, Tos can induce cytotoxic effect on BBI-differentiated prostate cancer stem cells. Therefore, the combination of BBI and TOS can lead to apoptosis of cancer stem cells.

Can MTHFR C677T SNP affect anti-mesothelioma effect via ER stress?

Momoka Fusegi[1], Ayami Sato[2], Kakeru Kohno[1] and Tomohiro Yano[1]

[1] Graduate School of Food and Nutritional Sciences, Toyo University
[2] School of Veterinary Medicine and Animal Science, University of Sao Paulo

Background: Malignant mesothelioma (MM) is characterized by poor responsiveness to current chemotherapeutic drugs difficult to cure. Thus, this malignant tumor is highly required a new treatment. In this study, we considered that more effective can be obtained by proposing a treatment method according to single nucleotide polymorphism (SNP). Methylene tetrahydrofolate reductase (MTHFR) C677T SNP promotes the accumulation of homocysteine (Hcy) and endoplasmic reticulum (ER) stress. However, excessive stress induces autophagy at the same time with apoptosis. Since Hcy is known as a factor causing ER stress, the difference in Hcy concentration due to SNP may cause a difference in anti-MM effect. Although it was revealed that the tocotrienol succinate ether derivative (T3E) induces ER stress, the association with the SNP is unknown.

Aim: To investigate the difference of the SNP contribute to the difference of apoptosis in MM cells via ER stress and autophagy.

Methods: We selected H28 cells as MTHFR wild type and H2452 cells as MTHFR hetero type by PCR-RFLP method. Cell viability was measured by WST-8 assay, levels of mRNA and protein were determined by qRT-real-time PCR and Western blotting, respectively.

Results: T3E induced ER stress and autophagy in both cell lines. However, mRNA level of CHOP, a key molecule to determine induction apoptosis by ER stress, showed a suppressive tendency in H2452. On the other hand, there was little difference on cell viability between two cell lines by T3E.

Conclusions: These results suggested that the presence of SNP was resistant to cell death via ER stress. It is considered that although Hcy is a factor that causes the resistance, T3E is expected to stronger anti-MM effects which doesn't depend on MTHFR SNP.

MICROGLIAL RESPONSES TO SYNGENEIC GLIOBLASTOMA IN A 18-KDA TRANSLOCATOR PROTEIN (TSPO) KNOCKOUT

RB Banati[1,2], P Wilcox[2], R Xu[2], G Yin[2], E Si[2], ET Son[2], M Shimizu[2], RMD Holsinger[2], A Parmar[1], D Zahra[1], A Arthur[1], R Middleton[1], GJ Liu[1], MC Gregoire[1] and Manuel Graeber[2]

[1] ANSTO
[2] University of Sydney

Background: The highly malignant glioblastoma (GBM) is the most common primary brain tumour. GBM cannot be completely resected. Less than half of GBM patients survive beyond a year. Clinical trials outcomes remain highly unsatisfactory, indicating that the basic understanding required for successful "translational research" has not yet been reached. One neglected determinant of glioma growth are microglia, the brain's resident macrophages, first shown by us (Grasbon-Frodl et al., Jahrestagung-Neuroonkologische-Arbeitsgemeinschaft, Deutschen Gesellschaft fuer Neurochirurgie, Dresden, 6-7 November 1998). However, the mechanisms by which microglia modulate glioblastoma growth remain unclear.

Aim: Development of an experimental system for studying the interactions between microglia, microglia-derived macrophages and glioma cells and visualising host-tumour interactions by PET imaging.

Methods: We have used a global 18-kDa translocator protein (TSPO) knockout mouse (Banati et al., DOI:10.1038/ncomms6452) and the selective TSPO ligand [18F]PBR111 for the *in vivo* study of glioma-host microglia interactions following intraparenchymal implantation of GL261 glioma cells (NCI Tumor Repository) enabling background-free tumor imaging.

Results: TSPO was expressed by implanted experimental glioblastoma as evidenced *in vivo* by [18F]PBR111 signals delineating the entire tumor volume without any appreciable signal in the TSPO-/- host tissue. Experimental glioblastoma were detectable in pre-symptomatic stages whereby the inherently high biological signal-noise ratio (TSPO+/+ tumour in a TSPO-/- surrounding tissue) provided an unprecedented contrast allowing detection of signals in small volumes (<1mm^3 range). Histological analysis demonstrated the expected close microglia-glioma interactions in controls. In TSPO knockout brains the histological association of host microglia with glioma appeared less pronounced and possibly qualitatively different.

Conclusions: Ongoing histological analysis suggests that TSPO is needed for normal microglia-glioma interactions. Inhibition of microglia through targeting TSPO should be explored as a new therapeutic avenue for interfering with glioblastoma growth. The TSPO+/+ tumour in a TSPO-/- host is a robust experimental approach to investigate invasive tumors without confounding signals from the host tissue.

Therapeutic inhibition of MYCN by targeting AKT activity in neuroblastoma.

Marion Le Grand[1], Kathleen Kimpton[1], Chelsea Mayoh[1] and Maria Kavallaris[1]

[1] Children's Cancer Institute

Neuroblastoma is the most common extra-cranial malignancy in children. Poor prognosis is strongly linked to MYCN amplification, which occurs in 25% of neuroblastoma patients. More than half of children diagnosed with *MYCN* amplification either do not respond to first-line therapy or develop acquired resistance. There is therefore an urgent need to identify new targetable molecular vulnerabilities and develop more efficient and less toxic treatments for neuroblastoma patients.

The AKT pathway is known to regulate MYCN expression through GSK3□, providing a rationale for AKT inhibition as a therapeutic strategy to target MYCN. Our study addressed the role of AKT in neuroblastoma pathophysiology and whether the AKT inhibitor perifosine can be a promising anti-cancer drug in neuroblastoma.

Our data revealed that high gene expression of AKT1 and AKT2 was significantly associated with poor outcome in neuroblastoma patients. RNAi-mediated depletion of AKT isoforms demonstrated that inhibition of total AKT activity rather than expression of particular isoforms was necessary to cause a significant decrease in neuroblastoma cell proliferation. Using either gene silencing or pharmacological inhibition, targeting AKT activity led to a significant downregulation of MYCN expression. In a pharmacological study, low perifosine concentration was able to increase the efficacy of first line therapy in *MYCN*-amplified neuroblastoma. Moreover in an *in vivo* model of neuroblastoma using low drug concentrations to avoid drug toxicity, combined perifosine with vincristine resulted in prolonged median survival as compared with either drug alone. These results demonstrate that perifosine can be used as a conventional drug sensitiser for *MYCN*-amplified neuroblastoma.

Collectively, this project may lead to the design of novel therapeutic strategy in *MYCN*-amplified neuroblastoma, which remains an aggressive and drug refractory disease. Focusing on perifosine, already in clinical trials, and anticancer drugs currently used in the clinic, our results have the potential to be fast tracked to the clinic.

Strengthening Multidisciplinary Performance in Cancer Services in Western Sydney: One Year on.

Lynleigh Evans[1], Brendan Donovan[1] and Paul Harnett[1]

[1] Western Sydney Local Health District

Introduction: While multidisciplinary team meetings (MDMs) are well-established in many institutions, there is wide variation in how they function and in their role in decision-making. This study adopts an innovative methodology to assess multidisciplinary team (MDT) performance and engage teams in performance improvement strategies.

Methods: The study protocol comprises a survey to evaluate MDM members' perceptions of their team's performance before the implementation of the program and annually on an ongoing basis; and a tumour program maturity matrix designed as a self-assessment tool showing five levels of maturity across 20 domains. Each MDM used the matrix to collectively assess its performance and identify priority areas for improvement

Results: The first survey has been completed and the second survey is nearing completion. 129 member surveys from 12 MDMs were completed in the first round and 95 responses have been received so far from the second survey. Overall improvement has been impressive with 22 of 25 (88%) questions with positive/negative answers showing improvement and a mean improvement of 39%. Some questions such as "does the team have Terms of Reference showed marked improvement (16% to 43%). All the teams completed the matrix in year one with results confirming that there was marked variation in performance between teams. Feedback showed, however, that the method of delivery needed to be simplified and digitised. This is now being embarked upon.

Conclusions: This study fills a gap in the literature by describing a means of improving performance from an organisational perspective. It differs from others in that it targets all tumour streams within the organisation and provides a framework by which MDMs can determine areas for improvement, while allowing considerable flexibility in the activities each team chooses to address.

The MDM survey and maturity matrix provide an excellent means not only for teams to identify their strengths and weaknesses but also for management to review its performance against standardised criteria and to identify priority areas for improvement and further support.

UNRAVELLING THE TUMOUR MICROENVIROMENT OF GLIOMA

Kelly McKelvey[1], Amanda Hudson[1,2], Helen Wheeler[1,3,2], Connie Diakos[4] and Viive Howell[5,6]

[1] Bill Walsh Translational Cancer Laboratory, The University of Sydney Northern Clinical School, Faculty of Health and Medicine; Northern Sydney Local Heath District Research (Kolling Institute); Sydney Vital Translational Research Centre, at Royal North Shore Hospital, St Leonards, NSW 2065, Australia
[2] The Brain Cancer Group, North Shore Private Hospital, St Leonards, NSW 2065, Australia
[3] Mark Hughes Foundation, Hunter Medical Research Institute, New Lambton Heights, NSW 2305, Australia
[4] Northern Sydney Cancer Centre, Royal North Shore Hospital, St Leonards, NSW, Australia
[5] Bill Walsh Translational Cancer Research Laboratory, Kolling Institute, Northern Sydney Local Health District, St Leonards, NSW 2065, Australia
[6] Northern Clinical School, Faculty of Medicine and Health, University of Sydney, Sydney, NSW 2006, Australia

Introduction: With the incidence and mortality of brain cancer almost equivocal there is a vital need to understand the intricacies of the glioma microenvironment.

Aim: To quantify the temporal and spatial localisation of immune cell populations and mediators during glioma development using the murine orthotopic Gl261 glioma model.

Methods: Mice were stereo-tactically inoculated with $1x10^6$ Gl261 cells at AP0.1mm, ML1.0mm, DV2.4mm Bregma. Immune cell populations were assessed at D0, D1, D3, D7, D14, D21 post-inoculation by veterinary haematological analyser (Coulter Ac·Tdiff™) and 16-parameter flow cytometry (Fortessa™).

Results: Significant temporal changes were observed in all immune cell populations among the splenic, bone marrow and peripheral blood systemic compartments: WBCs, RBCs, platelets, $CD3^+$ T cell, $CD3^+CD4^+$ Th, $CD3^+CD4^+CD25^+$ Treg, $CD3^+CD8^+$ Tc, $NK1.1^+$ NK, $NK1.1^+CD3^+$ NK/T, $CD115^+CD11b^+$ monocyte, $CD115^+CD11b^+CD80^+$ M1, $CD115^+CD11b^+CD206^+$ M2, $CD115^-CD11b^+$ DC, $CD115^-CD11b^+Ly6C^{high}Ly6G^-$ M-MDSC, $CD115^-CD11b^+Ly6C^+Ly6G^+$ PMN-MDSC, $CD117^+$ HSC and $CD19^+$ B cell (Kruskal-Wallis with Dunn's multiple comparison test; $p=0.02$- $p<0.0001$).

Analysis of plasma coagulation and inflammatory mediators, and histopathology of the tumour microenvironment is to be completed.

Conclusion: The data derived provides baseline characteristics to study the changes associated with radiation, chemotherapy and immunotherapy treatment and to sequence therapies to maintain immune modulation. This information will contribute to identifying those immunotherapies which will have maximal benefit among the glioma patient population, where currently anti-CTLA-4 and anti-PDL-1 immunotherapies have had little impact.

Identification of novel therapeutics for colorectal cancer using mass cytometry

Diana Shinko[1], Helen McGuire[2], Miguel Castañeda[1], Scott Byrne[3], Connie Diakos[4,5,6], Stephen Clarke[4,5,6] and Kellie Charles[1]

[1] Discipline of Pharmacology, Sydney Medical School, The University of Sydney, Sydney, NSW, Australia
[2] Discipline of Pathology, Sydney Medical School, The University of Sydney, Sydney, NSW, Australia
[3] Discipline of Infectious Diseases and Immunology, Sydney Medical School, The University of Sydney, Sydney, NSW, Australia
[4] Northern Sydney Cancer Centre, Royal North Shore Hospital, St Leonards, NSW, Australia
[5] Sydney Medical School, The University of Sydney, Sydney, NSW, Australia
[6] Bill Walsh Translational Research Laboratories, Kolling Institute of Medical Research, St Leonards, NSW, Australia

Introduction: An enhanced understanding of the immune-tumour interaction has led to significant clinical benefit in the use of immunotherapy in cancer. In colorectal cancer, however, a lack of understanding of the immune cell complexity means that the correct drug targets for exploitation remain elusive.

Aim: Our aim was to investigate the immune phenotype and inflammatory signalling pathways in colorectal cancer patients undergoing chemotherapy to identify novel immunotherapeutic targets.

Methods: Peripheral blood of 10 advanced colorectal cancer patients undergoing chemotherapy and 9 healthy volunteers was collected and analysed using Helios™, a Cytometry by Time-of-Flight (CyTOF) system (Fluidigm).

Results: Using a 35-marker panel, we quantified 7 major circulating immune cell types and over 20 subtypes. We found significant difference in major B cell populations and sub-populations of T cells (including regulatory T cells, central memory T helper cells and effector memory cytotoxic T cells) between the patients and the healthy volunteers. Further interrogation of B cell sub-populations are underway. We also quantified nine phosphorylated intracellular signalling markers. At baseline, results show that pP38 and pSTAT3 are significantly decreased in patients across the majority of immune cells whereas pSTAT5 is increased. Results also show that phosphorylated markers, such as pERK, can be activated following a cycle of chemotherapy and remain activated throughout the therapy. Relationships between immune profiles and clinical outcomes are currently being explored.

Conclusion: The use of mass cytometry has allowed the investigation of the immune profile of CRC patients and potential novel immunotherapeutic targets have been identified to improve clinical outcomes.

The development of a metal-based complex with anti-metastatic activity in breast cancer cells in vitro

Andria Yaourtis[1], Aviva Levina[1] and Peter Lay[1]

[1] The University of Sydney

Background: Cancer metastasis is the leading cause of death amongst cancer patients. Previous work from our research group has demonstrated that treatment of MDA-MB-231 cells (a highly aggressive human breast cancer cell line *in vitro*) with a metal-complex induces a morphological change in these cells, shifting them from a metastatic phenotype to a less aggressive one.

Aim: The aim of our research was to investigate the molecular mechanisms underlying the change in morphology of MDA-MB-231 cells after treatment with a metal-complex, and to characterise and quantify the extent and type of morphological change.

Methods: MDA-MB-231 cells were treated with a sub-toxic concentration of the metal- complex, and after 72 hours confocal laser scanning microscopy (CLSM) with immunofluorescence was used to characterise protein biomarkers for metastatic and epithelial cells. CLSM was also used to quantify changes in cell metrics and parameters post treatment. Scanning electron microscopy (SEM) and transmission electron microscopy (TEM) were used to determine changes in the surface topography and ultrastructure of cells. Further, isoelectric cell focusing (ICF) was used to investigate the effects of the metal complex on a cell signalling pathway that is significant in cancer.

Results: CLSM revealed changes in cell parameters including volume and surface area of cells post treatment, and SEM further confirmed an enlargement and flattening of these cells. Changes in protein phosphorylation indicating changes in the cell signalling cascade was evident with ICF.

Conclusion: This study provides a promising novel drug that has the ability to change the phenotype of aggressive metastatic cancer cells to a less invasive one.

Translational significance: The development of a drug targeting cancer metastasis will have profound clinical implications in the treatment of highly aggressive cancers.

Lymphoma in Border Collies: Survey results and genetic investigations

Pamela Soh[1], Katrina Cheng[1], Peter Bennett[1] and Peter Williamson[1]

[1] The University of Sydney

Background: Lymphoma is a common haematological malignancy in humans and in dogs. Dogs are an excellent model for human lymphoma as canine lymphoma exhibits important similarities including molecular abnormalities and treatment response to the disease. Recent research has identified potential risk regions for lymphoma in the Bullmastiff and Golden Retriever breeds. Border collies are a popular breed in Australia, but little research has explored the incidence of lymphoma or genetic associations to the disease in the breed.

Aim: To describe the results of a survey on the health status of Australian Border Collies, examine heritability and relationships between lymphoma-affected dogs, and investigate genetic associations with the disease.

Methods: Surveys were distributed to breeders/owners of Australian Border Collies. Survey questions included the current health status (healthy/ill/deceased) of the dog, pedigree information, and further clinical questions if the dog had lymphoma. Pedigree information was used for kinship cluster analysis and heritability estimation. DNA was extracted from blood samples and genotyped on the Illumina CanineUHD BeadChip, assaying 230,000 evenly distributed markers for genome-wide association analyses.

Results: Survey data revealed 57 out of 246 Border Collies were affected by lymphoma with a mean age of diagnosis at 9.16 years (SD ± 3.43) and multicentric, high grade B-cell lymphoma as the most common form. Pedigree analyses identified a degree of familial clustering of the disease, including a common female ancestor for 28 cases. The heritability estimate based on survey data for lymphoma was 0.04 (SE ± 0.19). No genetic associations for lymphoma were found on previously reported risk regions in other breeds on chromosome 5 and 13.

Conclusions: There is a relatively large number of lymphoma cases in Border Collies, and incidence in family groups suggests a heritable component. Importantly, the genetic risk for lymphoma appear unique between Golden Retrievers, Bullmastiffs, and Border Collies.

Survivorship care plans and cancer survivors' patient-reported outcomes: A meta-analysis

Rebecca E. Hill[1,2], Joanna E. Fardell[1,2], Richard J. Cohn[1,2], Claire E. Wakefield[1,2], Mary-Ellen E. Brierley[1,2], Emily Kothe[3], Kate Hetherington[1,2] and Rebecca Mercieca-Bebber[1,2,4]

[1] School of Women's and Children's Health, UNSW Sydney
[2] Behavioural Sciences Unit, Kids Cancer Centre, Sydney Children's Hospital
[3] School of Psychology, Deakin University
[4] NHMRC Clinical Trials Centre, The University of Sydney

Background: The Institute of Medicine recommends survivorship care plans (SCPs) as part of cancer survivorship care. Previous reviews have suggested that SCPs do not impact patient-reported outcomes (PROs), but no meta-analysis had been conducted.

Aim: Our meta-analysis compared PROs between SCP intervention and no SCP (control) conditions for adult and childhood cancer survivors. Our systematic review also examined the feasibility of implementing SCPs in survivorship care from the perspective of survivors and healthcare professionals.

Methods: We searched seven online databases from inception to 22 April 2018. Eligible articles for the meta-analysis included randomized controlled studies comparing survivors' patient-reported outcomes for SCP recipients versus controls, and the systematic review included articles assessing SCP feasibility. Following data extraction by two authors, we conducted random effects meta-analyses for each patient-reported outcome, using R version 3.4.0.

Results: Of 4,832 identified articles, 8 studies were eligible for the meta-analysis (n=1,286 cancer survivors) and 50 for the systematic review (n=18,949 survivors, n=3,739 healthcare professionals). Our meta-analysis found no significant difference between SCP intervention and control groups at 6-months post-intervention on physical functioning (g=-0.037, 95%CI[-0.17, 0.09]), satisfaction with information provision (g=0.131, 95%CI[-0.02, 0.28]) and self-efficacy (g=0.019, 95%CI[-0.22, 0.26]). There were also no significant differences between groups at 12-months post-intervention on anxiety (g=-0.008, 95%CI[-0.26, 0.24]), depression (g=0.030, 95%CI[-0.16, 0.23]), cancer-specific distress (g=-0.036, 95%CI[-0.17, 0.09]) or satisfaction with survivorship care (g=-0.030, 95%CI[-0.16, 0.10]). Our systematic review provides preliminary evidence for the feasibility of using SCPs and their potential positive impact on cancer survivors' adherence to medical recommendations and healthcare professionals' survivorship care knowledge. These results were consistent between studies on adult and childhood cancer survivors.

Conclusion: SCPs appear to be feasible but do not improve cancer survivors' PROs. Research is needed to ascertain whether this is due to SCP ineffectiveness, implementation issues or inappropriate PRO selection.

Salivary gland tumours and mobile phone use: fact or fiction?

Keshini Vijayan[1] and Guy Eslick[1]

[1] The University of Sydney

Background: There are conflicting epidemiological data on the relationship between mobile phone use and the development of salivary gland tumors.

Aim: To investigate the potential link between mobile phone use and the subsequent development of salivary gland tumors in a meta-analysis.

Methods: A comprehensive literature search of PubMed, EMBASE, Cochrane and Google Scholar was conducted. No restrictions were set on publication date or language. Studies were qualitatively assessed using the Newcastle-Ottawa scale.

Results: Seven studies with 1247 cases and 8935 controls were analysed. Overall, there was no significant association between the use of mobile phones and salivary gland tumors (OR=1.06; 95% CI: 0.86-1.32; I^2=0.00, p=0.60). Sub-analysis of analog phones (OR=0.92, 95% CI: 0.63-1.36; I^2=0.00, p=0.99), digital phones (OR=1.04, 95% CI: 0.72-1.51; I^2=0.00, p=0.87), ipsilateral use (OR=1.07, 95% CI: 0.84-1.36; I^2=0.00, p=0.74), and contralateral use (OR=0.90, 95% CI: 0.64-1.27; I^2=46.91, p=0.15), were also not found to be associated with developing salivary gland tumors. There was no evidence of publication bias (p=0.99).

Conclusion: Our findings indicate no significant association between mobile phone usage and salivary gland tumours. However, there was a critically important limitation within these studies, as all contained inadequate definitions of mobile phone use and assessment of mobile phone use. The published data is completely flawed and should not be relied upon as the observed result is not be an accurate estimate of the true carcinogenic risk of mobile phones, especially for heavy long-term users. This is an excellent teaching point for students undertaking epidemiological studies. The importance of exposure measurement and the correct definitions used are vital to determining the true risk. Therefore, in order to examine the long-term effects of heavy mobile phone usage associated with salivary gland tumor development, future research will require high quality and well-designed epidemiological studies to determine the true relationship.

Embedding Research (and Evidence) in Cancer Healthcare - EnRICH

Bea Brown[1], John Simes[2], Michael Boyer[3,1], Phillip Hogg[4,1], Anthony Joshua[5,6,7] and Jane Young[8,9,10]

[1] Sydney Catalyst, University of Sydney
[2] NHMRC Clinical Trials Centre, University of Sydney
[3] Chris O'Brien Lifehouse
[4] Centenary Institute, University of Sydney
[5] St Vincent's Hospital
[6] The Kinghorn Cancer Centre
[7] Garvan Institute of Medical Research
[8] School of Public Health, University of Sydney
[9] RPA Institute of Academic Surgery, Sydney Local Health District
[10] Surgical Outcomes Research Centre (SOuRCe), Sydney Local Health District

Background: Lung cancer is the most common cause of cancer death in Australia, accounting for nearly 20% of all cancer deaths, and is a leading cause of morbidity and burden of disease. The Australian Institute of Health and Welfare estimates more than 12,700 Australians will be diagnosed with lung cancer in 2018 and nearly 9,200 will die from the disease. The outlook for patients with lung cancer is poor, with only a 16% overall five year survival rate. For patients diagnosed with advanced stage disease, five year survival decreases to only 1%. Improvements in lung cancer survival rates are not comparable with improvements for other cancers.

Aim: The aim of the Sydney Catalyst Embedding Research (and Evidence) in Cancer Healthcare "EnRICH" program is to assemble a patient cohort to: describe the natural history of and patterns of care for lung cancer; identify current gaps in evidence and practice for clinical quality improvement; create a platform for researchers across the T1-T3 translational research spectrum to develop and initiate clinical research and intervention studies to address gaps. Initially lung cancer will be an exemplar.

Methods: EnRICH is a prospective clinical cohort of a minimum 1000 lung cancer patients from Sydney Catalyst metropolitan, regional and rural member clinical sites, including archival tumour tissue and serial blood samples with matched demographic, clinical, biomarker, molecular profile, and outcome data (including quality of care and patient-reported outcomes). The cohort will enable reliable estimates of outcomes both overall and within histologic and genetic sub-types.

Results: This poster will present preliminary descriptive analyses for the first 250 patients in the cohort, including patient, disease and treatment data to identify initial priorities for linked translational research studies and quality improvement interventions.

Conclusions

N/A

Evaluation of artificial intelligence software for automated data extraction within the NSW Cancer Registry

Sheena Lawrance[1], Clair Cooke-Yarborough[1], Vidur Mahindra[1], Maria Arcorace[1] and Chau Bui[1]

[1] Cancer Institute NSW

Background: With increasing information and data being submitted to NSW Cancer Registry (NSWCR) in electronic format, there is an organizational need to innovate existing NSWCR applications. Submission of electronic data provides an opportunity to automate data processing within the NSWCR and reduce the time required to abstract cancer data. Automating of data processing steps has the potential to produce more current, accurate, quality and robust data for conducting epidemiological studies which directly inform cancer health plans and policies.

Information from electronic pathology reports collected by NSWCR are routinely abstracted (coded) manually. NSWCR recently implemented Artificial Intelligence (AI) software designed to auto- code electronic pathology reports.

Aim: This project aims to evaluate the ability for auto-coding AI software to improve efficiency of operations as well as data quality within the NSWCR context.

Methods: We will investigate the effectiveness of using AI software within three scenarios: (i) auto-coding of prostate cancer pathology reports, (ii) rapid identification of triple-negative breast cancers from pathology reports and flag these for review, and (iii) identification of additional clinical data items for collection in colorectal cancer pathology reports. Under each scenario, we will measure similarities and discrepancies between auto-abstractions and manual data extractions.

Results: The project is in the commencement stage and we will present preliminary results, as well as discuss the process and methodology used to evaluate the AI software and its application in a population-based cancer registry.

Conclusion: The findings of this study will demonstrate the utility of AI software solutions to improve the efficiency of data collection for clinical data items within a population-based cancer registry. This will help drive cancer system change by optimizing the timeliness and quality of cancer data available for research and policy development.

Use of a modified Tumour-Node-Metastasis staging system in the New South Wales Cancer Registry, Australia

Sheena Lawrance[1], Claire Cooke-Yarborough[1], Vidur Mahindra[1], Maria Arcorace[1] and Chau Bui[1]

[1] Cancer Institute NSW

Background: Tumor Node Metastasis (TNM) stage group is either not reported or under-reported in Population-based Cancer Registries (PBCRs) despite being an important variable for epidemiological analyses. Registry-Derived (RD) staging was developed in collaboration with Cancer Australia and the Victorian Cancer Registry to provide the best estimate of TNM at diagnosis using routine data sources available to Australian PBCRs. In 2017, Australian PBCRs, including NSWCR, participated in an initiative to estimate RD stage for prostate, colorectal, breast, lung and melanomas diagnosed in 2011. This project was supported by Cancer Australia through an initiative to strengthen national data for reporting cancer stage at diagnosis, treatments and recurrence (the STaR project). While completing STaR, NSWCR performed steps to manually stage TNM (considered the gold-standard staging system). In addition, Degree of Spread (DoS), a less-specific summary staging measure, is consistently collected in the NSW Cancer Registry (NSWCR).

Aim: Evaluate the potential for RD-stage to be used in place of DoS or TNM in epidemiological studies.

Methods: We mapped (i) RD-stage to TNM, and (ii) RD stage to DoS, through consultation with a registered pathologist. Test characteristics (concordance, Cohen's kappa, sensitivity, specificity) were calculated to compare RD stage with TNM and DoS. We considered performance metrics >80% as acceptable.

Results: A total of 25,209 cases were selected into the study. For breast and melanoma, high agreement (>80% for all performance metrics) between RD stage and TNM were achieved across all stage groups. Greater variability in agreements were observed for other tumor groups. Our DoS analysis is in the commencement stage.

Conclusion: Stage at diagnosis provides valuable information for cancer planning and policy. We identify and quantify specific caveats for using RD stage as a proxy for TNM and DoS. Our research highlights limitations and potential benefits of using readily available stage variables.

Salicylic acid downregulates UHRF1 and exerts anti-cancer activity in CaSki cells

Harsimran Sidhu[1] and Neena Capalash[2]

[1] Department of Biotechnology Panjab University
[2] Department of Biotechnology Panjab University India

BACKGROUND: Worldwide, 530 000 new cases and 270 000 deaths annually are attributed to cervical neoplasm. Repurposing of FDA approved drugs for cancer treatment is an incredibly exciting idea. Clinical and experimental data suggests that prolonged use of nonsteroidal anti-inflammatory drugs (NSAIDs) primarily aspirin reduces the risk of various cancers such as breast, gastric and colorectal. Salicylic acid, a primary metabolite of aspirin has been cited as a major product responsible for pharmacological effects of aspirin. Ubiquitin-like with PHD and RING Finger domains 1 (*UHRF1*) acts as a fundamental regulator of cell proliferation and epigenetic machinery**.** UHRF1 has been reported to be over-expressed in many malignancies including cervical cancer.

AIM: To get mechanistic insight to anti-cancer effects of salicylic acid on CaSki cells.

METHODOLOGY: MTT reduction assay, real time PCR, western blotting, colony formation, scratch assay, flow cytometry, fluorescence microscopy and siRNA transfection assays were performed.

RESULTS: Salicylic acid (150 μM) resulted in significant (P<0.05) downregulation of *UHRF1* in CaSki cells. Reduced expression of UHRF1 correlated with 67% reduction in colony forming ability of CaSki cells and cell cycle arrest at G1 phase with concomitant upregulation of *p53* and *p21*. Silencing of UHRF1 also resulted in increased expression of *p53* as well as *p21* suggesting involvement of *UHRF1* in exerting anti-cancer effects of salicylic acid. Presence of cells in sub G1 phase and apoptotic bodies indicated apoptosis induction. Salicylic acid treatment also reduced migration of CaSki cells. Upregulation of *FANCF*, *E-cadherin* and *TIMP-2* (hypermethylated tumor suppressor genes) and downregulation of proangiogenic factor, *VEGF* further highlighted anti-cancer potential of salicylic acid. Salicylic acid resulted in insignificant changes on viability of normal epithelial (fr-2) cells indicating its selective action on neoplastic cells.

CONCLUSION: Downregulation of *UHRF1* by salicylic acid acts as one of the mechanism behind its anti-cervical cancer effects.

CD146 contributes the metastatic properties of human colon adenocarcinoma cells

Takumi Yamazaki[1] and Kazunori Kato[1]

[1] Department of Biomedical Engineering, Toyo University.

CD146 (MCAM) expressed on not only vascular endothelial and smooth muscle cells but also various malignant tumor cells. It has been shown that overexpression of CD146 predicts poor prognosis of solid tumor. Several reports using transfectants or gene silencing technique have shown that CD146 is involved in cell adhesion and inflammatory cell migration. However, contribution of CD146 in tumor metastasis is still controversial. In order to investigate the effect of CD146 on tumor metastatic properties, we establish two subclones from DLD-1 (human colon adenocarcinoma cells) expressing CD146 or not. Both cell lines express epithelial tumor marker EpCAM and TROP2 equally, while CD146 (+) DLD-1 could only express CD44 variant v8-v10 and EphA2. Using metabolic assay by Alamarblue and ATP-Glo, we found enhanced metabolism and decreased lactate production in CD146 (+) DLD-1. Consist with the morphological changes to mesenchymal features CD146 (+) DLD-1, the expression of E-cadherin and claudin-3 in tight junction were decreased in CD146 (+) DLD-1 compared to CD146 (-) DLD-1. In addition, CD146 (+) DLD-1 significantly increased the production of VEGF and the induction of various genes (*slug*, *twist* and *zeb1*) which are involved in epithelial to mesenchymal transition (EMT). Next, we aimed to induce mesenchymal to epithelial transition (MET) in CD146 (+) DLD-1 using several phytochemical agents. We found that treatment of CD146 (+) DLD-1 by resveratrol could reverse the morphology to epithelial phenotype and downregulate CD146 expression slightly. Moreover, resveratrol restored the expression of claudin-3 and inhibited the expression of *slug* and *snail*. These data indicate that expression of CD146 contributes in EMT, and resveratrol might be an effective candidate for treatment of aggressive feature of CD146 expressing tumors.

High Expression of MYC in Diffuse Large B-Cell Lymphoma in Bullmastiff

MengJia Chen[1]

[1] University of Sydney

Introduction: DLBCL (diffuse large B cell lymphoma) is the most common lymphoma/hematopoietic neoplasm in both dogs and humans. According to our previous research, five SNPs (single nucleotide polymorphisms) on CFA13 are believed to be associated with early onset lymphoma in bullmastiff; interestingly, these mutations locate near a proto-oncogene MYC and a region syntenic to human PVT1. MYC and PVT1 have been suggested to play roles together in malignancies while MYC is also recognised as a new prognostic indicator of cancer for humans.

Aim: Human and canine lymphoma are strikingly similar in many aspects including symptoms, pathological traits, molecular levels and response to chemotherapy. Therefore, dogs have become a popular subject for comparative oncology. Through our study, we are hoping to help both sides to find the secret and cure lying in the genes.

Method: 15 samples including lymph nodes and mass tissues of cases of lymphoma in bullmastiff, were tested with IHC (immunohistochemistry) staining to determine the level of expression of MYC.

Result: We expect high expression of MYC in these samples and with that result, will carry out further research that could hopefully explain the relations and interactions between MYC and PVT1 in canine lymphoma where there is no current study focusing on.

Note: The experiment is still in progress and the data has not been fully interpreted but we are very keen to attend the conference and are pretty confident that we will accomplish the study by then.

Nobiletin synergizes cytotoxicity of antimicrotubule agents by inhibiting Pin1 pathway

Kazunori Kato[1], Masaaki Honma[1] and Takumi Yamazaki[1]

[1] Department of BioMedical Engineering, Toyo University

Nobiletin is a citrus-derived polymethoxy flavonoid that suppresses cell proliferation, angiogenesis and metastatic properties in various cancer cells. In this study, we investigated the combined effects of nobiletin and various chemotherapeutic agents on the cytotoxicity of human colon and esophageal cancer cell lines. We cultured cancer cells at serial dilution of chemotherapeutic agents with or without nobiletin and assessed cell cytotoxicity at 5 days after drug treatment. The addition of a suboptimal dose of nobiletin did not alter the growth of cancer cells, however antitumor effect of antimicrotubule agents such as docetaxel, paclitaxel, vincristine and MMAE were significantly enhanced by the combination of nobiletin. In contrast, nobiletin attenuated cytotoxic effect of antimetabolites (gemcitabine and 5-FU) and DNA-platinating agent (cisplatin). Moreover, enhanced cytotoxicity by nobiletin was also verified in the combination with MMAE- or DM1-conjugated antibodies against EpCAM and EphA2. We found the inhibition of phosphorylation and nuclear translocation of Pin1 (peptidyl-prolyl isomerase) and cyclin-D1 by nobiletin, suggesting a rational molecular target of nobiletin is Pin1. Overall, these data suggest that nobiletin might useful for the chemotherapeutic treatment of microtubule inhibitors.

The complexity of families: Young adults and their families' communication about BRCA1 and BRCA2 cancer risk

Alison Young[1], Phyllis Butow[2], Paul Rhodes[1], Katherine Tucker[3,4], Rachel Williams[3,4], Emma Healey[5], Claire Wakefield[6,7] and Nicole Bartley[8]

[1] School of Psychology, The University of Sydney, Sydney, NSW, Australia
[2] Psycho-oncology Co-operative Research Group, School of Psychology, The University of Sydney, NSW, Australia
[3] Hereditary Cancer Clinic, Department of Medical Oncology, Prince of Wales Hospital, Sydney, NSW, Australia
[4] Prince of Wales Clinical School, UNSW, Sydney, NSW, Australia
[5] Illawarra Shoalhaven Cancer & Haematology Network, NSW, Australia
[6] School of Women's and Children's Health, UNSW, Sydney, NSW, Australia
[7] Behavioral Sciences Unit Proudly Supported by the Kids with Cancer Foundation, Kids Cancer Centre, Sydney Children's Hospital, Randwick, Australia
[8] University of Sydney

Background: While family communication about a BRCA 1 or BRCA2 gene mutation is a catalyst for the uptake of risk-reducing measures in young adults, disseminating information within families and across generations is complex.

Aim: This study aimed to explore how young adults and their families communicate about a BRCA1/2 gene mutation, from a family system perspective.

Methods: In-depth family interviews and questionnaires (N=68 individuals; 21 families) were completed at three hospital sites in Australia. Data involved thematic analysis using family systems theory.

Results: Five key themes were identified and explored: 1) Family communication was driven by a sense of responsibility to ensure the health of family members, which could result in open disclosure or protective non-disclosure. 2) This responsibility was generally held by women in the family, since a BRCA 1 or BRCA2 status was generally seen as a woman's problem. 3) Family culture influenced disclosure. Family members with close relationships and commonalities were more likely to share information. 4) Significant life-stage and health-related events such as a cancer diagnosis prompted communication. 5) Family identities were solidified through the incorporation of a gene mutation in family scripts, while members of the family who held differing views to their families expressed less agreeableness and openness to disseminate information.

Conclusions: The utilisation of family therapy skills in routine practice is considered essential. Understanding potential barriers that arise from family members holding differing views to their family offers insight for future research inquiry and areas of further training and clinical support.

FUTURE BURDEN OF CANCER IN AUSTRALIA ATTRIBUTABLE TO CURRENT MODIFIABLE BEHAVIOURS

Maarit A Laaksonen[1], Maria E Arriaga[1], Karen Canfell[2], Robert MacInnis[3], Peter Hull[1], Emily Banks[4], Graham G Giles[3], Paul Mitchell[5], Robert G Cumming[5], Julie E Byles[6], Dianna J Magliano[7], Jonathan Shaw[7], Anne Taylor[8], Tiffany K Gill[8], Vasant Hirani[5], Julie Marker[9], Sue McCullough[10], Elizabeth Klaes[11], Louiza S Velentzis[12], Barbara-Ann Adelstein[1] and Claire M Vajdic[1]

[1] University of New South Wales
[2] Cancer Council NSW
[3] Cancer Council Victoria
[4] Australian National University
[5] University of Sydney
[6] University of Newcastle
[7] Baker Heart and Diabetes Institute
[8] University of Adelaide
[9] Cancer Voices South Australia
[10] Lung Foundation Australia
[11] Breast Cancer Network Australia
[12] Cancer Council New South Wales

Background: Estimates of the future burden of cancer preventable through modifications to current exposure distributions, and the distribution of such burden across population subgroups, are lacking.

Aim: To i) assess the future burden of cancer in Australia preventable through modifications to current behaviours, and ii) compare the distribution of the preventable cancer burden between population subgroups.

Methods: We linked pooled data from seven Australian cohort studies (N=367,058) to national cancer and death registries, and estimated the strength of the associations between behaviours and cancer incidence and death using an adjusted proportional hazards model. We estimated exposure prevalence from contemporary national health surveys. We combined these estimates to assess the future burden of cancer preventable through individual and joint exposure modifications by calculating Population Attributable Fraction (PAFs) and their 95% confidence intervals, using a novel method accounting for competing risk of death and statistically comparing PAF differences between population subgroups.

Results: During the first 10 years of follow-up, there were 22,078 deaths and 27,483 incident cancers, including 2,025 lung, 3,471 colorectal, 640 premenopausal and 2,632 postmenopausal breast cancers. The leading preventable cause for lung cancer is current smoking (PAF = 53.7%), for colorectal and postmenopausal breast cancer body fatness (PAF = 11.1% and 12.8% respectively), and for premenopausal breast cancer regular alcohol intake (PAF = 12.6%). Physical inactivity, unhealthy diet and hormonal factors also contribute to the future burden of some of these cancers. The cancer burden attributable to modifiable exposures is markedly higher in certain population subgroups, including men (lung, colorectal), people with risk factor clustering (lung, colorectal, breast), and individuals with low educational attainment (lung, breast).

Conclusions: Our results on the preventable cancer burden in Australia and the population subgroups with the highest preventable burden can inform timely public health action to improve health and health equity.

Differentially expressed Triple negative breast cancer-specific genes and their association with prognosis.

Mamta Pariyar[1,2], Kelly Kiejda[1,2] and Rodney Scott[3,4,5]

[1] Priority Research Centre for Cancer Research, Innovation and Translation, School of Biomedical Sciences and Pharmacy, Faculty of Health and Medicine, University of Newcastle
[2] Hunter Medical Research Institute
[3] Priority Research Centre for Cancer Research, Innovation and Translation, School of Biomedical Sciences and Pharmacy, Faculty of Health and Medicine, University of Newcastle, NSW, Australia.
[4] Hunter Cancer Research Alliance, and Cancer research program, Hunter Medical Research Institute, NSW, Australia.
[5] Pathology North, John Hunter Hospital, New Lambton Heights, NSW, Australia.

Background: Triple negative breast cancer (TNBC) is a highly metastatic and aggressive subtype of breast cancer which lacks hormonal receptors-estrogen receptor, progesterone receptor and the overexpression of HER2 protein. There are no targeted therapies for this breast cancer subtype, therefore, chemotherapy and surgery remain the only options for treatment. Previous studies from our laboratory (Mathe et al., 2015. Sci Rep 5: 15832) have identified four genes (ANKRD30A, ANP32E, DSC2 and IL6ST) that are differentially expressed between normal and breast cancer tissues; and between TNBC and hormone receptor positive breast cancer subtypes. These results were validated in two independent cohorts, with one of these genes (IL6ST) being associated with overall survival in TNBC patients.

Objectives: The aim of the current study is to validate the TNBC-specific expression of these genes and define their association with survival in a larger cohort. Additionally, the role of these genes in proliferation, migration and invasion will be determined.

Methods: Digital Droplet PCR was used to quantitate the expression of these genes. KM Plotter was used to determine the association of these genes with survival in publicly available datasets.siRNA has been used to knockdown the expression of these genes to determine their role in proliferation, migration and invasion.

Results: KM Plotter analysis has shown that high expression of ANKRD30A, DSC2 and IL6ST was associated with increased relapse-free survival (RFS), whilst high expression of ANP32E was associated with significantly worse RFS. Digital Droplet PCR analysis of expression and correlation with survival in a cohort of 148 breast cancer specimens and functional analysis in TNBC cell lines is ongoing and will be presented.

Conclusion: This study has the potential to identify ways in which these TNBC-specific genes could be utilised as predictive markers in identifying a subpopulation of TNBCs with worse outcome.

The Effect of the Wuzhi Tablet on the Metabolism of Dabrafenib in Human Liver Microsomes

Alia Fahmy[1], Alan Boddy[1] and Xiaoman Liu[1]

[1] The University of Sydney School of Pharmacy, Faculty of Medicine and Health

Background: 25 to 50% of cancer patients use complementary and alternative medicines, often alongside conventional chemotherapeutic agents, which may result in herb-drug interactions.

Commercial extracts of *Schisandra sphenanthera,* referred to as "Wuzhi" tablets or capsules, are used in Traditional Chinese Medicine to treat hepatitis, inflammatory disease, and cancer. Wuzhi and several of its bioactive lignans, including Schisantherin A and Schisandrol B, affect the *in vivo* and *in vitro* metabolism of substrates for drug metabolising enzymes.

Dabrafenib is a serine-threonine kinase inhibitor used in the treatment of $BRAF^{V600E}$-mutated unresectable or metastatic melanoma. Dabrafenib is taken orally and chronically by patients in an unsupervised setting and undergoes CYP450-mediated metabolism. These factors make dabrafenib potentially vulnerable to herb-drug interactions.

Aim: The aim of this study was to investigate the effect of Wuzhi tablet extract (WZE), Schisantherin A, and Schisandrol B on the metabolism of dabrafenib in human liver microsomes.

A secondary aim was to quantify the content of Schisantherin A in WZE.

Methods: Liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS) was used to quantify the formation of hydroxy-dabrafenib from dabrafenib using human liver microsomes, including any inhibitory effect of WZE, Schisantherin A, or Schisandrol B.

LC-MS/MS was also used to quantify Schisantherin A in WZE.

Results: WZE and its lignans inhibited the metabolism of dabrafenib in a concentration-dependent manner. Schisandrol B was a more potent inhibitor (IC_{50} = 0.36 μM) than Schisantherin A (IC_{50} = 43 μM) and WZE (IC_{50} = 0.65 μM based on Schisantherin A content).

Schisantherin A content in WZE tablets was calculated to be 16.8 mg per gram of tablet powder (2.14 mg/g).

Conclusions: The results of this study indicate that a herb-drug interaction between dabrafenib and Wuzhi is possible due to inhibition of CYP450-mediated metabolism, however further work is required to elucidate the clinical relevance. Until the clinical risk can be evaluated, patients should be advised to avoid the combination.

Genomic prediction in the management of cancer: canine lymphoma model

Victor Wei Tse Hsu[1], MEHAR KHATKAR[1], Imtiaz Randhawa[1], Pamela SOH[1] and PETER WILLIAMSON[1]

[1] The University of Sydney

Cancer is a common cause of mortality in dogs. One of the most common forms of canine cancer is lymphoma, a cancer of lymphocytes, which accounts for up to 25% of cancer cases. Lymphoma in dogs is in most cases treatable but not curable, with more aggressive forms leading to rapid decline and death within 1-6 months. There are a number of studies that provide evidence of an association of lymphoma and breed, e.g. in the Boxer, Bullmastiffs, Golden Retriever, Cavalier King Charles Spaniels, and Border Collies.

Genetics research has increased rapidly with high throughput molecular biology tools and analytical approaches. Genotype data has provided insights into many questions about cancer risk factors for a wide range of species based. While the development of tumours have been largely investigated, the molecular basis of specific risk factors is still largely unclear.

Simulations of trait-specific genome-wide scans is developed base on SNP data to compute composite selection signals (CSS) by multiple information from: 1) in-house genotype datasets, 2) published canine genotype datasets and 3) canine phenotype dataset.

The overall objective of these studies is to generate outcomes that may contribute to development of a high-throughput, low-cost test for cancer in dogs.

A genetic variant in telomerase gene modifies cancer risk in Lynch syndrome patients harbouring MSH2 mutations

Bente Talseth-Palmer[1,2,3], Tiffany-Jane Evans[3], Sami Belhadj[4], Katherine Bolton[3], Shanite Jagmohan-Changur[5], Juul Wijnen[5,6], Hans F.A. Vasen[7], Laura Valle Velasco[4] and Rodney Scott[8,9,10]

[1] Department of Clinical and Molecular Medicine, Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology, Trondheim, Norway
[2] Research and Development Unit, Møre og Romsdal Hospital Trust, Molde, Norway
[3] School of Biomedical Science and Pharmacy, Faculty of Health and Medicine, University of Newcastle and Hunter Medical Research Institute, Newcastle, Australia
[4] Hereditary Cancer Program, Catalan Institute of Oncology, IDIBELL and CIBERONC, Hospitalet de Llobregat, Barcelona, Spain
[5] Deparment of Human Genetics, Leiden University Medical Center, Leiden, The Netherlands
[6] Department of Clinical Genetics, Leiden University Medical Center, Leiden, The Netherlands
[7] Department of Gastroenterology and Hepatology, Leiden University Medical Center, Leiden, The Netherlands
[8] Medical Genetics, Hunter Medical Research Institute
[9] Priority Research Centre for Cancer, School of Biomedical Sciences and Pharmacy, Faculty of Health and Medicine, University of Newcastle
[10] Hunter Area Pathology Service, John Hunter Hospital

Background: Individuals with Lynch syndrome (LS), an autosomal dominant inherited cancer syndrome caused by mutations in DNA mismatch repair genes have an increased risk of developing a range of epithelial malignancies, but a pre-malignant phenotype does not exist. Common genetic variants of the TERT gene are influencing telomere length and have been associated with a wide range of cancers, including CRC and LS.

Aim: In this study we have chosen to genotype 3 SNPs in *TERT*; rs2736108 (upstream gene variant), rs2075786 and rs7705526 (both intronic variants), previously shown to influence telomere length or association with LS.

Methods: We genotyped 1895 LS patients samples for rs2075786 (G>A) and 1241 LS patient samples for rs2736108 (C>T) and rs7705526 (C>A) using TaqMan SNP assays (Applied Biosystems). Risk of LS cancer with each SNPs genotype was estimated by heterozygous and homozygous odds ratio (OR) using simple logistic regression and mixed-effects logistic regression to adjust for gene, gender and country taking into account family ID (probands and relatives).

Results: We see an increased risk of LS cancer for the patients carrying *MSH2* mutations and the heterozygous genotype (GA) for rs2075786 (OR=1.84, confidence interval (CI) =1.15-2.94), p=0.01). This association is even stronger if we divide the group into LS cancer <45 years of age at diagnosis and compare it to LS cancer free patients; *MSH2* and GA for rs2075786 (OR=2.53, CI=1.43-4.49, p=0.002).

Conclusion: Even though both *MLH1* and *MSH2* mutation carrier's starts off with the same risk of cancer, a SNP in *TERT* is associated with a differential risk of developing cancer for *MSH2* mutation carriers. By including modifier gene/loci in risk algorithms it should be possible to tailor surveillance options for individual patients, which should allow for better outcomes in terms of patient uptake resulting in reduced morbidity and mortality.

Mechanisms of balance impairment in cancer survivors with chemotherapy-induced peripheral neuropathy

J. Matt McCrary[1], David Goldstein[1], Hannah Timmins[2], Tiffany Li[2], Terry Trinh[1] and Susanna Park[2,1]

[1] UNSW Sydney
[2] The University of Sydney

Background: Chemotherapy-induced peripheral neuropathy (CIPN) is a significant side effect of chemotherapy treatment - estimated to affect 30-40% of cancer survivors, resulting in numbness and tingling in the extremities and increased falls incidence in affected patients. Balance assessment is used to quantify relative falls risk and can provide vital insights regarding the mechanisms of increased falls incidence in CIPN and thus an evidence base to inform the design of rehabilitative interventions.

Aim: Investigate the relationships between CIPN and quantitative balance deficits.

Methods: Cancer survivors (N=163; 57 male; 56.9±12.7 years) 3-months to 5-years post-treatment (mean 12.6±11.6 months post-treatment) with neurotoxic chemotherapies attended for a single assessment of patient-reported CIPN (EORTC CIPN-20), objective CIPN (Total Neuropathy Score, clinical) and balance (Swaymeter). Balance was quantified by tracking patients' centre of mass (greater movement=reduced stability) during quiet standing with eyes open and closed on solid and foam surfaces. Linear regression analyses (Bonferroni-Holm correction) were used to determine the relationship between balance and CIPN severity. ANOVAs were used to determine the relationship between CIPN symptoms, patient-reported balance and strength deficits, and objective balance measures.

Results: The majority of patients reported CIPN symptoms (68%, N=111) - severity: mild=61.3%; moderate=29.7%; severe=9.0%. Increasing patient-reported and objective CIPN symptoms were correlated with reduced balance performance across all conditions ($.32 \leq r \leq .56$; $p < .0001$). Relationships remained significant when controlling for age ($p < .01$). Patients who reported CIPN symptoms but not impairments in strength ($p < .01$) or balance ($p < .03$) demonstrated impaired postural stability in test conditions with eyes closed but not with eyes open.

Conclusions: Increasing balance impairment is linked to increasing CIPN symptoms, independent of age effects. CIPN has an especially deleterious impact on balance when visual feedback is removed, indicating that proprioceptive deficits associated with CIPN may be key effectors of falls risk in CIPN patients and a target for rehabilitative interventions.

6-shogaol alone and in combination with platinum drugs have shown significant activity against ovarian cancer cell lines

MD SHEIKH ANWAR[1], Jun Qing Yu[2], Philip Beale[3] and Fazlul Huq[1]

[1] The University of Sydney
[2] Discipline of Biomedical Science, School of Medical Sciences, Sydney Medical School, University of Sydney
[3] Concord Cancer Centre

Backgrounds: Ovarian cancer is known as one of the dreaded diseases across the globe. It is treated mainly by platinum drugs given alone or in combination with paclitaxel. However problems of drug resistance that is often acquired still remains. While resistance to platinum drugs can be due to over expression of NF-κB, AKT/PKB and other pathways, it is believed that phytochemicals and other natural compounds can hinder their expression.

Methods: IC_{50} values of compounds were first determined before combination studies. Studies on DNA damage, cellular platinum accumulation and Pt-DNA binding levels were also carried out. Proteomics study has been performed aiming to determine key proteins associated with drug resistance.

Results: 6-shogaol (IC_{50}: 6.79-10.20 μM) showed significant activity against ovarian cancer cell lines compared to cisplatin (IC_{50}: 1.18-9.02 μM). In addition, 6-shogaol showed synergism in combination with cisplatin and oxaliplatin when administered as a bolus 0/0h and with 0/4 h sequence against the cell lines. Moreover, concurrent administration of cisplatin and 6-shogoal produced higher cellular platinum accumulation and three times greater Pt-DNA binding than cisplatin in parent ovarian A2780 cell line. Furthermore, 6-shogaol in combination with cisplatin also showed increased Pt-DNA binding in A2780cisR cell line. Also, proteomic studies have been performed to explore the proteins involved with drug-resistance in ovarian cancer cisplatin-resistance $A2780^{cisR}$ and picoplatin-resistance $A2780^{ZD0473R}$ cell lines.

Nineteen proteins were found to be significantly expressed applying to 23 spots in untreated $A2780^{cisR}$ and $A2780^{ZD0473R}$ cell lines compared to the level observed in untreated parent A2780 cell line. 6-shogaol in combination with cisplatin and oxaliplatin was found to reduce expression of anti-apoptotic proteins and heighten that of pro-apoptotic proteins in ovarian $A2780^{cisR}$ and $A2780^{ZD0473R}$ cell lines, thus providing an explanation for synergistic action.

Conclusion: Overall, it could be seen that ginger derived phytochemical, 6-shogaol administered alone and in combination with cisplatin and oxaliplatin shows significant activity against ovarian cancer tumour models so that 6-shogaol could be a prospective candidate for combination therapy to manage ovarian cancer in the future.

Mechanisms underpinning resistance to CDK4/6 inhibition and endocrine therapy in ER+ breast cancer

Sarah Alexandrou[1,2], Neil Portman[3], Christine Lee[3], Kristine Fernandez[3], Heloisa Helena Milioli[1], Elgene Lim[3,4] and C. Elizabeth Caldon[1,2]

[1] Cancer Division, Garvan Institute of Medical Research, Sydney, NSW, Australia
[2] St. Vincent's Clinical School, Faculty of Medicine, UNSW, Sydney, NSW, Australia
[3] The Kinghorn Cancer Centre, Garvan Institute of Medical Research, Sydney, NSW 2010, Australia.
[4] St. Vincent's Clinical School, Faculty of Medicine, UNSW Sydney, NSW 2052, Australia.

Background: Endocrine resistant estrogen receptor positive (ER+) breast cancers are particularly dependent upon cyclin-dependent kinases (CDK) 4/6 for proliferation. As such, potent CDK4/6 inhibitors (CDK4/6i) have been integrated into clinical practise for treatment of advanced ER+ breast cancers. Despite initial efficacy, acquired resistance to CDK4/6i is already emerging by mechanisms which remain unknown.

Aim: To develop clinically relevant *in vitro* and *in vivo* tumour models of CDK4/6i and endocrine therapy to understand and identify the mechanisms of acquired resistance in breast cancer.

Methods: Using MCF-7 breast cancer cells we have generated a palbociclib resistant (PalbR) cell line. To complement this, we are developing a panel of *in vitro* and *in vivo* models that mimic the clinical treatment of patients. Here, palbociclib is combined with an endocrine therapy, tamoxifen, fulvestrant, or long-term estrogen deprivation to mimic aromatase inhibition. Furthermore, we have developed a patient-derived xenograft model resistant to chronic fulvestrant and palbociclib treatment. We will perform comprehensive analyses such as RNA-seq, flow cytometry and western blotting to identify resistance mechanisms that are unique and common to each treatment regime.

Results: We have identified several potential mechanisms of palbociclib resistance whereby increased proliferation was induced by an increase in estrogen-response genes and a reduction of the CDK inhibitor proteins p21 and p27. We demonstrate that PalbR cells remained sensitive to treatment with endocrine therapy. Mechanistically, loss of p27 de-represses CDK2 activity, and we show that PalbR and MCF-7 cells resistant to combined palbociclib and tamoxifen therapy have enhanced sensitivity to the CDK2 inhibitor CYC065. Furthermore, ß-galactosidase assays revealed a decreased induction of senescence.

Conclusions: Our novel panel of acquired resistance models demonstrate differences in cellular morphology and growth trajectories, and our analysis has identified mechanisms of CDK4/6i resistance and provides insight into novel therapeutic combinations.

Oral THC/CBD cannabis extract for chemotherapy-induced nausea and vomiting (CINV): Trial in progress

Antony Mersiades[1], Annette Tognela[2], Paul S Haber[3], Martin Stockler[4,5,6], Nicholas Lintzeris[3,7], John Simes[1,8], Iain McGregor[9], Ian Olver[10], David J Allsop[11], Craig Gedye[12], Adrienne Kirby[1], Rachael L Morton[1], Anh D Tran[1], Karen Briscoe[13], Peter Fox[14], Morteza Aghmesheh[15], Nicole Wong[1], Anjali Bhardwaj[1] and Peter Grimison[1,8]

[1] NHMRC Clinical Trials Centre, University of Sydney
[2] Macarthur Cancer Therapy Centre, Campbelltown, NSW, AUSTRALIA
[3] Sydney Medical School, University of Sydney, Camperdown, NSW, AUSTRALIA
[4] Concord Cancer Centre, Concord Hospital, Concord NSW
[5] University of Sydney
[6] NHMRC Clinical Trials Centre, Sydney Medical School, University of Sydney, Sydney, Australia
[7] Drug and Alcohol Services, South East Sydney Local Health District, Concord, NSW, AUSTRALIA
[8] Chris O'Brien Lifehouse, Camperdown
[9] Lambert Initiative for Cannabinoid Therapeutics, University of Sydney, Camperdown, NSW, AUSTRALIA
[10] Sansom Institute for Health Research, University of South Australia, Adelaide, SA, AUSTRALIA
[11] Lambert Initiative for Cannabinoid Therapeutics, University of Sydney
[12] Department of Medical Oncology, Calvary Mater Newcastle, Newcastle, NSW, AUSTRALIA
[13] Mid-North Coast Cancer Institute, Coffs Harbour Hospital, Coffs Harbour, NSW, AUSTRALIA
[14] Central West Cancer Care Centre, Orange, NSW, AUSTRALIA
[15] Illawarra Cancer Care Centre, Wollongong, NSW, AUSTRALIA

Background: Up to half of patients receiving chemotherapy of moderate or high emetic risk experience CINV despite optimal anti-emetic prophylaxis. Limited evidence suggests cannabinoid medicine in the form of tetrahydrocannabinol (THC) may reduce CINV, and addition of cannabidiol (CBD) may improve efficacy and tolerance.

Aim: The aim of this multi-centre, randomised, placebo-controlled, phase II/III trial is to determine efficacy and cost-effectiveness of addition of an oral cannabinoid-rich THC/CBD cannabis extract for control of CINV.

Methods: Target population is adult patients experiencing CINV during moderately and highly emetogenic chemotherapy regimens despite appropriate anti-emetic therapy, who are scheduled to receive at least 2 more consecutive cycles (A, B and, where applicable, C). Treatment consists of oral THC 2.5mg/CBD 2.5mg (Tilray TN-TC11M) capsules or placebo TDS on days -1 to 5, in addition to guideline-consistent anti-emetics, including rescue medications. Patients will start with 1 capsule PO TDS and can dose-titrate to a maximum of 4 capsules PO TDS based on nausea control and side-effects. In the pilot trial (N=80), subjects are randomised for cycle A, cross-over for cycle B, and nominate preferred treatment for cycle C. The planned definitive trial (N=250) will randomise subjects to investigational product or placebo for cycles A, B and C in a parallel design. The primary end-point is the proportion of patients gaining a complete response (no emesis and no use of rescue medications) (0 - 120h), with additional end-points of (i) complete response, (ii) no emesis, (iii) no significant nausea and (iv) no use of rescue medication during the a) acute, b) delayed, and c) overall phases of cycle A, B and C, (iv) adverse events, (v) quality of life, and (vi) cost-effectiveness.

As of 25/05/2018, 52 of 80 participants recruited.

Results: Pre-results

Conclusions: NA

Funding: NSW Department of Health.

Acknowledgements: Trial participants, investigators and research staff. Drug supply by Tilray.

ACTRN: 12616001036404

The Needs of Young People After the Death of a Family Member to Cancer: Validating the Bereaved Cancer Needs Inventory

Richard Tindle[1], Fiona McDonald[1,2], Pandora Patterson[1,2] and Daniel Costa[2]

[1] CanTeen, Sydney, NSW, Australia
[2] The University of Sydney, NSW, Australia

Background: Adolescents and young adults (AYAs; aged 12-25yrs) who experience the death of a parent or sibling to cancer can have elevated levels of psychological distress, which are strongly related to their unmet psychosocial needs. To identify their unmet needs, we developed the Bereaved Cancer Needs Inventory (BCNI). By understanding the needs of bereaved AYAs we can provide individualised support to help reduce their distress.

Aim: We aimed to i) provide a descriptive analysis of the psychosocial needs of AYAs who have experienced the death of a parent or sibling to cancer; ii) identify how their unmet needs are related to their levels of psychological distress; iii) to validate the psychometric properties of the BCNI.

Methods: A total of 335 AYAs completed the BCNI - a 58 item questionnaire measuring unmet needs across eight domains (*information, time-out and recreation, practical assistance, support from other young people, support, dealing with feeling, and family*) and the Kessler-10 psychological distress scale.

Results: Participants indicated several unmet psychosocial needs (offspring: $M = 27.26$, $SD = 16.87$; siblings: $M = 22.86$, $SD = 17.30$) which were strongly correlated with their levels of psychological distress (offspring: $r\ (265) = .58$, $p < .001$; siblings: $r\ (35) = .64$, $p < .001$). For the BCNI, a factor analysis indicated a 7-factor solution and we reduced the number of items in the scale to 37. Item response theory analysis indicated the BCNI was a reliable measure and could discriminate between those with low and high unmet needs.

Conclusion: The BCNI is the first psychometrically validated instrument to measure the unmet psychosocial needs of bereaved AYAs. We argue that health care professionals should use the BCNI to identify psychosocial risk factors of distress in bereaved AYAs and tailor support to the individual.

Proteomics confirms low uPAR expression superimposed on KRAS mutation carrying cells can negate many of cancer hallmarks

Seong Beom Ahn[1], Abidali Mohamedali[1], Dana Pascovici[1], Subash Adhikari[1] and Mark Baker[1]

[1] Department of Biomedical Sciences, Macquarie University

Cancer metastasis is the primary cause of mortality. To date molecular mechanisms underpinning it remain elusive. Metastasis is propagated by driver mutations in oncogenes and suppressors genes (e.g., KRAS, BRAF, APC, PTEN, SMAD4, PIK3CA, AKT1 and TP53), accompanied by passenger mutations and underlying genomic instability. To understand the biological processes involved, a unifying framework developed by Hanahan and Weinberg, called the '*hallmarks of cancer*' (HoC) organizes unique complexities of cancer. HoCs include; (1) sustaining proliferative signaling, (2) activating invasion/metastasis, (3) resisting cell death, (4) enabling replicative immortality, (5) inducing angiogenesis, (6) evading growth suppression, (7) deregulating cellular energetics metabolism, (8) avoiding immune destruction, (9) tumour-promoting inflammation and (10) genome instability/mutation. Underlying these HoCs, genome instability generates mutational genomic diversity, with inflammation amplifying the HoCs. Recognizing how critical interacting node protein expressions changes impact HoCs will accelerate cancer therapeutic development.

In this study, we asked if decreased expression (↓~44%) of the lynchpin protein urokinase plasminogen activator receptor (uPAR) in HCT116^{ASuPAR} cells negates HoCs - reversing changes driven by a KRAS and PIK3CA mutant background. Comprehensive proteome coverage (whole cell lysis combined with 2 membrane extraction methods) encompassed a broad and significant number of HoC - driven biochemical pathways. Coupling Ingenuity pathway analysis with in-house bioinformatics, demonstrated that ↓uPAR expression negates some pathway in each of the HoCs, that the majority are associated with invasion/metastasis, resisting cell death or sustaining proliferation. This result closely parallels a uPAR search in a PubMed text mining engine called CHAT (Cancer Hallmarks Analytics Tool). uPAR expression changed expression of known metastasis-related and uPAR interacting membrane proteins like EGFR, caveolin, vitronectin and integrins. Collectively, we show uPAR is a critical lynchpin capable of altering signaling pathways that regulating the HoC in a 'classical' colorectal cancer mutational background cell model (e.g., HCT116).

Sensitivity testing of CTCs to chemotherapeutic agents as a predictor of therapeutic response and clinical outcome

Joachim Fluhrer[1], Dorothea Schott[2], Monika Pizon[3], Ulrich Pachmann[2] and Katharina Pachmann[3]

[1] Genostics
[2] SIMFO
[3] Laboratory Pachmann

Background: Circulating Tumour Cells (CTCs) are cancer cells that have detached from the primary tumour, migrated through the extracellular matrix and invaded the bloodstream. It is now well established that these cells represent the haematogenous route of metastatic progression. Due to the inherent instability of cancer cells, CTCs may be heterogenous to cells of the primary tumour and thus have an alternate sensitivity profile to the primary cancer, rendering them potentially resistant to treatment of therapeutic intent. Enrichment and analysis of CTCs represent what is now being heralded as a *liquid biopsy.*

Aim: To evaluate the predictive capacity of pre-treatment testing of chemotherapeutic agents CTCs in terms of correlation with tumor response and relevance to clinical outcome.

Methods: CTCs among the other cells from the peripheral blood of patients were exposed *in vitro* to chemotherapeutic agents selected for treatment, prior to the commencement of therapy. The agent's capacity to induce apoptosis in varying concentrations and for different incubation times was measured. The extent of apoptosis observed was compared to the post-treatment reduction of CTCs *in vivo* and to clinical outcome such as relapse-free survival or disease progression.

Results: Sensitivity testing of CTCs of 35 patients was performed as per the following distribution: Breast cancer (20), ovarian cancer (4), colon cancer (6) prostate cancer (3), pancreatic cancer (2), lung cancer (1), melanoma (1)

There was a high correlation between *in vitro* sensitivity of CTCs and both *in vivo* CTC reduction and clinical outcome for all cancers ($p=0.005$)

Conclusion: In vitro pre-treatment testing of clinically-selected agents planned for cancer therapy against CTCs correlates highly to the *in vivo* sensitivity of CTCs and offers a high predictive value for clinical outcome. Further clinical trials are warranted.

Role of long noncoding RNA TUG1 in liver cancer

Xiaoqi Huo[1], Jacob George[1] and Liang Qiao[2]

[1] Westmead Institute for Medical Research, University of Sydney and Westmead Hospital
[2] Storr Liver Centre, Westmead Institute for Medical Research (WIMR), the University of Sydney and Westmead Hospital, Westmead, NSW 2145, Australia

Background: Hepatocellular carcinoma (HCC) is a leading cause of cancer related death worldwide. Drug resistance and tumour recurrence significantly contribute to the poor prognosis of this malignancy. Long noncoding RNAs (lncRNAs) are a group of functional RNAs (>200nt in length) without protein coding ability. A large number of dysregulated lncRNAs have been identified and show a close relationship with liver cancer initiation, progression, and therapeutic outcomes. Our preliminary studies have shown that the lncRNA TUG1 is highly relevant to liver cancer formation, and thus could be a potential therapeutic target.

Aim: We aimed to study the biological role of TUG1 in HCC.

Methods: The expression pattern of TUG1 was tested in HCC tissues and adjacent non-tumourous liver (n=42), as well as in liver cancer cell lines by quantitative real time PCR (qPCR). The expression of TUG1 in two liver cancer cells (SNU182 and SNU423) was knocked down by specific siRNA against TUG1, and the impact of TUG1 downregulation on the proliferation, colony formation, migration and invasion ability of these cells was studied. Propidium iodide staining was used for cell cycle analysis.

Results: TUG1 was overexpressed in HCC tissue compared with adjacent non-tumourous liver ($p<0.001$). In two liver cancer cell lines (SNU182, SNU423), TUG1 was significantly up-regulated compared with a normal liver cell line (IHH). Silencing of TUG1 by siRNA markedly decreased the proliferation and colony forming ability of liver cancer cells ($p<0.05$). Knockdown of TUG1 reduced the ability of cancer cells to migrate ($p<0.05$) and invade ($p<0.05$) and led to cell cycle arrest at G0/G1 ($p<0.05$).

Conclusions: TUG1 is overexpressed in liver cancer. TUG1 may promote the progression of HCC by increasing cancer cell proliferation, migration and invasion. TUG1 may be a promising target for the treatment of liver cancer.

Dual inhibition of JAK and Src: A novel and promising therapeutic combination for pancreatic cancer

Ashleigh Parkin[1], Paul Timpson[1] and Marina Pajic[1]

[1] The Garvan Institute of Medical Research

Introduction: Pancreatic cancer (PC) has a 5-year survival of only 6%, and persists as the 4th most common cause of cancer-related death in Western societies. A more tailored treatment approach may be beneficial as the current standard-of-care therapies offer only a modest increase in overall patient survival. Recent large-scale genomic studies have revealed that the Src/JAK/STAT3 signalling pathway is deregulated in up to 35% of PC, and is yet to be systematically examined in this disease. Consequently, we hypothesized that targeting pancreatic tumours with activated JAK/STAT3 signalling with selective JAK1/JAK2 or JAK3 inhibitors and an Src inhibitor represents a promising novel therapeutic strategy for this disease.

Materials and methods: We utilized well-annotated patient-derived cell-line models (ICGC), along with cell-lines generated from the aggressive KPC mouse model. Using these pre-clinical models we assessed the *in vitro* efficacy of therapeutic strategies involving Src/JAK/STAT3 inhibition, using cell proliferation assays, 2D-drug synergy screens, and 3D organotypic invasion assays. Extracellular matrix integrity post-treatment was assessed using second-harmonic generation (SHG) imaging and picrosirius staining. To examine in vivo efficacy, we utilized a syngeneic KPC mouse model, and performed both orthotopic and subcutaneous studies.

Results: We show that selected JAK and Src-inhibitors inhibit cell proliferation in candidate PDCLs and KPC lines, characterized by activated Src/JAK/STAT3 signalling, with combination therapy being synergistic in the majority of these cell-lines. Cell invasion was significantly inhibited in organotypic matrices, and there was decreased collagen contractility, and reduced fibrillar collagen coverage. We also demonstrate the *in vivo* efficacy of these therapies, and show their ability to reduce regulatory T-cells, MDSCs and tumour-associated macrophages.

Conclusion: Our findings demonstrate the potential for tailored therapeutic strategies involving Src/JAK/STAT3 inhibition in PC, and suggest that therapeutic efficacy may be the result of targeting both tumour cells and the tumour microenvironment, as well as by overcoming tumour-induced immunosuppression.

Targeting CDK4/6 and mTOR alone or in combination in sarcoma cell lines

Xiaochun Wang[1], David Goldstein[2], Philip Crowe[1] and Jia-Lin Yang[1]

[1] University of New South Wales
[2] UNSW Sydney

Background: The phosphatidylinositide-3-kinase/Protein kinase B (AKT)/ mammalian target of rapamycin (mTOR) signaling is central for cancer growth, survival and motility. One of the key restraints on cell growth downstream is retinoblastoma (Rb) tumour suppressor, which is negatively regulated by the cyclin-dependent protein kinases (CDK) 4/6 protein. We hypothesize that blocking both the CDK4/6 and the mTOR allows the double brakes to tumour growth.

Aim: Our aim is to investigate whether combination therapy using mTOR and CDK4/6 inhibitors (palbociclib and ridaforolimus) would have a synergistic growth inhibitory effect in sarcoma.

Methods: The effect and mechanism of palbociclib and ridaforolimus was investigated in a panel of twelve sarcoma cell lines by Crystal-violet colorimetric and Western blot assays. HT1080 fibrosarcoma metastatic mouse model was investigated for *in vivo* therapeutic study.

Results: Palbociclib showed anti-proliferation in all cell lines (IC50s: 0.1 - 1.1uM), while ridaforolimus had growth inhibition in 10/12 cell lines (IC50s: 0.4-26nM). The palbociclib-ridaforolimus combination achieved synergistic effect (CIs: 0.1-0.9) in 9/12 cell lines, including applying the drugs in different sequence (together or pre-treatment with one drug for 24-48 hours) and ratio (1:1, 1:2, 1:4, 2:1 or 4:1). The Western blot demonstrated that the 2-drug combination further blocked both CDK/Rb/E2F and AKT/mTOR pathways, via promoting apoptosis. *In vivo*, combination therapy using palbocilib (10 and 30mg/kg, every other day) and ridaforolimus (0.1 and 0.3mg/kg, daily for 5 days per week) for 4 weeks synergistically (CI = 0.7) inhibited the development of lung metastases (mean number of colonies: 132 in low combination dose and 38 for high combination dose) compared to monotherapy [243 (palbociclib) and 255 (ridaforolimus) in low dose, 113 and 97 for high dose] and vehicle control (286).

Conclusions: This study demonstrated that palbociclib-ridaforolimus combination is active in a variety of sarcoma subtypes and worthy of further development towards a clinical trial.

Targeting adaptive metabolic reprogramming in pancreatic ductal adenocarcinoma to overcome chemotherapy resistance

Sarah Hancock[1], Dimitrios Stivaktas[1] and Nigel Turner[1]

[1] School of Medical Sciences, University of New South Wales

Background: Pancreatic ductal adenocarcinoma (PDAC) is the tenth most common cancer in Australia, yet it has one of the most dismal prognoses in modern medicine with a 5-year survival of just 7.7%. Contributing to the poor survivability of PDAC is its highly aggressive and chemoresistant nature, which is driven by genetic and phenotypic heterogeneity. Mutations in oncogenes result in wide-ranging effects on cell metabolism, allowing the cells to acquire metabolites necessary for rapid growth and proliferation. Cellular heterogeneity can aid the cancer cells in acquiring chemoresistance through adaptive metabolic reprogramming, in which chemotherapy action is circumnavigated by alternative metabolic pathways. Metabolomics has shown promise in being able to detect adaptive metabolic reprogramming in other cancers, and so we have applied this methodology to the study of chemoresistance in PDAC

Aim: The aim of this research was to comprehensively profile the metabolome of several pancreatic cancer cell lines to establish metabolic heterogeneity, and then identify any adaptive metabolic pathways that could contribute to chemotherapy resistance.

Methods: Liquid chromatography/mass spectrometry was used to achieve comprehensive metabolite profiling of several pancreatic cancer cell lines. Metabolites were identified using an online mass spectral database and confirmed by comparison with authentic standards. Metabolite profiling was also undertaken in pancreatic cancer cells after exposure to gemcitabine to determine any chemotherapy-driven adaptive metabolic reprogramming.

Results and Conclusions: Our method detected several hundred metabolites within each pancreatic cancer cell line, with detailed analysis identifying distinct metabolic profiles between the different cell lines. A number of metabolic pathways were found to be altered compared with noncancerous pancreatic cells, including metabolites involved in central carbon metabolism, glycolysis, glutaminolysis, nucleotide synthesis, and lipid synthesis. Metabolite profiling of gemcitabine-treated PDAC cells uncovered several potential adaptive metabolic pathways, and work is ongoing using stably labelled isotope tracing to further characterise these mechanisms of chemoresistance.

Investigating chemotherapy induced peripheral neuropathy in cancer survivors: an online patient survey

Eva Battaglini[1], David Goldstein[2] and Susanna Park[3]

[1] University of New South Wales
[2] UNSW Sydney
[3] Brain and Mind Centre, University of Sydney

Background: Chemotherapy-induced peripheral neuropathy (CIPN) is a major but poorly understood side effect of cancer treatment. CIPN can lead to cessation of effective treatment, long-term functional disability and reduced quality of life, yet at present there is little understanding of its impact.

Aims: This study aims is to investigate the impact of neurotoxic chemotherapy side effects on the lives of Australian cancer survivors.

Methods: An anonymous online survey was used to collect data on demographics, cancer diagnosis, cancer treatment, CIPN and other side effects of chemotherapy, including standardised measures of general health, quality of life, physical activity, pain and neuropathic symptoms.

Results: Data was analysed from 700 respondents (84% female, 16% male), mean age 58 years (*SD* 10.27). A majority of respondents were treated for breast cancer (60%), with 14% treated for colorectal cancer, 7% myeloma and 4% ovarian cancer. Chemotherapy types received included paclitaxel (31%), docetaxel (33%), oxaliplatin (13%) and thalidomide (6%).

The majority of respondents (80%) reported experiencing neuropathic symptoms after completing chemotherapy, with 76% reporting current CIPN. Patients completed chemotherapy 3.46 ± 3.26 years ago, and 34% of those who have experienced CIPN reported no improvement in symptoms since completing treatment. In respondents with current CIPN, functional impacts were seen: 29% reported moderate or severe difficulties with walking, and 24% reported moderate or severe difficulties with hand function. Respondents with current CIPN scored lower on quality of life than those without current symptoms, and reported greater limitations in daily life due to emotional distress.

Although no relationship was seen between reported exercise levels and CIPN, those who met Australian exercise guidelines had higher quality of life scores than those who did not.

Conclusions: These findings suggest that CIPN has a lasting impact on cancer survivors, supporting further work to improve assessment, prevention and treatment of this condition.

Health Outcomes Research

Viet Do[1], Weng Ng[1], Susannah Jacob[1], Geoff Delaney[1] and Michael Barton[1]

[1] Collaboration for Cancer Outcomes Research and Evaluation, Ingham Institute for Applied Medical Research, UNSW

AN ESTIMATION OF THE POPULATION-BASED SURVIVAL BENEFIT OF FIRST-COURSE CHEMOTHERAPY FOR CANCER

Background: Randomized clinical trials describe the benefit of chemotherapy for cancer patients with selected patient and disease characteristics. The overall survival benefits for the whole population of cancer patients in Australia, if evidence-based guidelines for chemotherapy were implemented, are unknown. This study's purpose was to estimate the overall population survival benefit of routinely-used chemotherapy with evidence-based practice.

Methods and Materials: Decision trees with evidence-based indications for chemotherapy have been previously defined. Each branch of the tree corresponds to a specific cohort who have, or do not have, defined indication for curative and palliative chemotherapy. Chemotherapy survival benefit was defined as the absolute incremental survival benefit of first-course chemotherapy over no chemotherapy (best supportive care) for palliative indications or over radiotherapy or surgery+/_ radiotherapy in curative indications. Multiple electronic citation databases were systematically queried, including Medline and Cochrane library. In cases where there were multiple sources of the same level of evidence, then hierarchical meta-analysis was performed. The survival benefits of chemotherapy were estimated for 1- and 5-year. To assess the robustness of our estimates, sensitivity analyses were performed.

Results: The estimated 1-year and 5-year absolute population-based overall survival benefits of optimally-used first-course chemotherapy for cancer were 5.6% (95% Confidence Interval, CI 4.5%-6.8%) and 4.1% (95% CI, 4.0%-4.2%) respectively.36% of survival benefit was attributed to first-course palliative chemotherapy. The 1-year survival benefit of the entire cancer population was mostly contributed from palliative indications.

Conclusion: Chemotherapy agents prolong life for cancer patients at 1-year and 5-years. Chemotherapy provides a modest survival benefit when it is used under guideline recommendations. It is essential to include other relevant quality of life-adjusted endpoints and patient-reported outcomes in future studies in this group of patients.

Discipline of Pharmacology, Sydney Medical School, The University of Sydney, Sydney, NSW, Australia

Madison Orr[1], Kellie Charles[1], Euan Walpole[2], Jennifer Martin[3], Sallie Pearson[4] and Connie Diakos[5]

[1] Discipline of Pharmacology, Sydney Medical School, The University of Sydney, Sydney, NSW, Australia
[2] Cancer Services Division, Princess Alexandra Hospital, Brisbane, QLD, Australia
[3] Clinical Pharmacology, The University of Newcastle, NSW, Australia
[4] Pharmacoepidemiology and Pharmaceutical Policy Research Group, The University of Sydney, NSW, Australia
[5] Northern Sydney Cancer Centre, Royal North Shore Hospital, St Leonards, NSW, Australia

Introduction: Systemic inflammation is found in 25% of metastatic colorectal cancer (mCRC) patients and is associated with a 50% reduction in overall survival. However, the mechanisms underlying systemic inflammation remain elusive.

Aims: This study aimed to investigate the effect of systemic inflammation on quality use of medicine and outcomes using a linked dataset of mCRC patients.

Methods: Records from Queensland's CHARM oncology prescribing database were linked to external QLD health data collections (blood counts, death records) from four hospital sites between 2009 and 2014. Statistical analysis was used to investigate validated inflammatory biomarkers and the prediction of drug utilisation and survival.

Results: 25% of the 487 patients with mCRC presented with elevated systemic inflammatory markers. Patients with high inflammation recorded a reduced overall survival (OS) compared with those with low inflammation (9.9 vs 23.8 months, $p < 0.0001$). As a cohort, patients with high inflammation received significantly less cycles of therapy within the first line, reduced first line duration and less lines of therapy overall. Such patients were also less likely to receive targeted biologics in the first line setting compared to patients with low inflammatory markers (27% vs 39%, $p = 0.07$). Patients with high inflammation receiving mono- and doublet therapy received less cycles, reduced first-line duration and less lines of therapy overall, while patients receiving triplet therapy recorded no differences in first-line drug dosing and scheduling. However, all three treatment groups recorded a significantly reduced OS for mCRC patients with high inflammation compared to patients with low inflammation.

Conclusion: The use of this novel linked-dataset has further substantiated the reduced survival outcomes in mCRC patients with high inflammation and highlighted their altered drug utilization. This data enhances our understanding of current treatments that can be optimised to improve survival for this high risk group.

Cognitive Difficulties for Women after Breast Cancer: Compounding Problems When Trying to Return to Work

Joanne Lewis[1] and Lynette Mackenzie[1]

[1] University of Sydney

Introduction: Women with breast cancer report cognitive difficulties during and after treatment. The cause of cognitive changes continues to be debated. It is estimated that 70% of women report cognitive changes and for some, the symptoms lasting up to 20 years. With the survival rates for breast cancer increasing, women have to manage these cognitive changes, whilst trying to return work.

Objectives: Firstly, to identify how a combination of problems related to cognitive changes after breast cancer impact on a woman's ability to perform her work tasks and participate in employment. Secondly, explore the potential role of occupational therapy in addressing cognitive changes at various points in the recovery process

Method: A scoping review was conducted to explore what is known about the issues contributing to difficulties performing work tasks and participating in employment for women with cognitive changes due to breast cancer.

Results: In early stages of breast cancer recovery, cognitive symptom recognition may be overlooked as medical professionals may be unaware intervention options. Formal cognitive assessments may not validate self-reported symptoms, or accurately identify task specific problems experienced. At work, women may hide their cognitive difficulties. Employers may feel ill - equipped to deal with such problems. Regardless of when cognitive changes are identified, there is little recognition of the role occupational therapy can play in providing ecologically valid assessments and interventions.

Conclusion: There are substantial opportunities for occupational therapists to provide workplace based cognitive assessments and interventions for women with breast cancer experiencing cognitive difficulties.

CD83 is a New Potential Biomarker and Therapeutic Target for Lymphoma

Xinsheng Ju[1], Ziduo Li[1], Edward Abadir[1], Kenneth Lee[2], Candice Clarke[2], Jennifer Hsu[1], Christian Byrant[1], Suzanne Pears[3], Neroli Sunderland[3], Scott Heffernan[3], Annemarie Hennessy[3], Tsun-Ho Lo[1], Geoffery Pietersz[4], Phillip Fromm[1], Pablo Silveira[1], Con Tsonis[1], Wendy Cooper[5], Ilona Cunningham[6], Christina Brown[2], Georgina Clark[1] and Derek Hart[1]

[1] Dendritic Cell Research, ANZAC Research Institute
[2] Department of Anatomical Pathology, Concord Repatriation General Hospital
[3] Animal Facility, Royal Prince Alfred Hospital
[4] Burnet Institute
[5] Tissue Pathology and Diagnostic Oncology, Royal Prince Alfred Hospital
[6] Department of Haematology, Concord Repatriation General Hospital

Background: Despite the advance of current treatment regimes, new targeted therapies for lymphoma are warranted, especially for refractory/relapsed patient. CD83 is a member of the Ig superfamily that is expressed as a membrane (mCD83) and a soluble molecule (sCD83). Our group first reported mCD83 expression on HRS cells of Hodgkin's lymphoma (HL). sCD83 was also detected in serum from HL and mantle cell lymphoma (MCL) patients.

Aims: The aim of this study is to assess whether CD83 is a potential biomarker and therapeutic target in HL and MCL patients, whether our human anti-human CD83 mAb (3C12C) and its toxin conjugate (3C12C-MMAE) can be potential therapeutic agents for lymphoma.

Methods: Immunohistochemical staining was performed on formalin fixed paraffin embedded lymph node biopsies of HL and MCL patients. The serum sCD83 level was monitored in HL patients during sequential treatment with chemotherapy. 3C12C and 3C12C-MMAE were tested for killing efficiency on lymphoma cell lines. Five non-human primate (NHP) received intravenous human-IgG or 3C12C mAb at days 0, 7, 14 and 21 as part of a toxicity trial.

Results: Most tumor cells in HL and MCL biopsies were CD83 positive. High levels of sCD83 were detected in HL patient sera and these returned to normal in patients who had good clinical responses to chemotherapy confirmed by positron emission tomography scans. 3C12C and its 3C12C-MMAE conjugate killed lymphoma cell lines. In a NHP trial with 3C12C, no toxicity was observed but there was evidence of CD83 positive target cell depletion in the lymph node.

Conclusion: CD83 is novel biomarker in some lymphoma patients. Anti-CD83 mAb and its toxin conjugate, killed CD83+ lymphoma cells *in vitro*. No toxicity was observed in a 3C12C dose-escalation NHP study. These data establish CD83 as a potential biomarker and therapeutic target in lymphoma.

Three-dimensional brain tumour models: a tool to advance the detection and treatment of Glioblastoma Multiforme

Annemarie Nadort[1,2], Sameera Iqbal[1], Mahsa Vaezzedah[1], Dmitry Polikarpov[1], Shivani Sachdev[1], Zahra Khabir[3], Yi Qian[1], Andrew Davidson[1], Nicolle Packer[1], Ewa Goldys[4] and Anna Guller[1]

[1] Macquarie University
[2] ARC Centre of Excellence for Nanoscale BioPhotonics
[3] macquarie university
[4] UNSW

Background: Successful clinical translation of techniques and therapies that advance the detection and treatment of high-grade brain cancer, glioblastoma multiforme (GBM), needs controlled, ethical and practical lab-based GBM models that accurately represent the biological reality. Traditional monolayer cell culturing is chemically and mechanically unauthentic, while organ-specific three-dimensional cell cultures can simulate tumour tissues more closely.

Aim: In this work, we aim to develop and characterize a three-dimensional model of GBM created by tissue engineering methodology.

Methods: We obtained acellular brain tissue scaffolds by decellularization, seeded them with human GBM (U251 and U87) and control undifferentiated rat neurons (PC12) cells ($2 \cdot 10^5$ cells/mm^3), and cultured the resulting 3D tissue engineering constructs (TECs) for up to 4 weeks in vitro. We microscopically assessed the hallmarks of tumour progression in TECs in comparison to conventional monolayer cultures, as well as the GBM-specific conversion of 5-Aminolevulinic acid (5-ALA) to the fluorescent compound Protoporphyrin-IX (PpIX), a feature used for fluorescence-guided surgery.

Results: We successfully created 3D *in vitro* living equivalents of glioma tissue. GBM and normal brain cells demonstrated different invasion potential (U251 > U87 >> PC12): the tumour cells grew more rapidly and populated the scaffolds completely in 2 weeks, while PC12 cells occupied the outer surfaces of the scaffolds in 7 days after which they proliferated minimally. The organ-specific environment affected both growth kinetics and cellular morphology in a cell line-specific manner. Incubation of the TECs with 5-ALA resulted in a clear PpIX fluorescent signal during confocal imaging.

Conclusions: We have developed and characterized a biologically accurate living 3D GBM model and demonstrated its capability to be used as a tool to study tumour biology and development of diagnostic technologies. Our model represents a sustainable approach to fill the gap between the conventional 2D cell cultures, animal studies and clinical trials.

Exploring pharmacological inhibition pathways in BRAF mutated colon cancer

Crystal Semaan[1,2], Benjamin Brown[2] and Mark Molloy[3]

[1] Centenary Institute, The University of Sydney
[2] Dept Molecular Sciences, Macquarie University
[3] Kolling Institute, Faculty of Medicine and Health, The University of Sydney

Background: Many colon cancers harbour mutation of *KRAS*, but approximately 10 % are driven by mutation in the serine/threonine kinase *BRAF* proto-oncogene. In BRAF melanoma and thyroid carcinoma, pharmacological inhibition of this pathway is clinically effective, but a trial in BRAF colon cancer was unsuccessful, with resistance likely due to compensation from EGFR and PI3K pathways. We have previously shown that CK2 kinase inhibition potentiates the anti-proliferative effect of BRAF inhibition in melanoma and thyroid cancers, and we are now testing this in colon cancer.

Aim: Evaluate the *in vitro* therapeutic utility of using CK2, EGRF or PI3K inhibitors to prevent proliferation in BRAF colon cancer.

Methods: Colon cancer cell lines (SW480, HT-29, Lim2405, Colo205) representing common genetic mutations were used for cell viability assays. Pharmacological inhibitors against CK2 (CX-4945), PI3K (GDC0941), EGRF (erlotinib), BRAF (dabrafenib) were tested.

Results: Addition of CK2 blocking agent with dabrafenib provided no improvement over single agent dabrafenib in BRAF colon cancers. However, CK2 inhibition combined with erlotinib improved the anti-proliferative activity in all cell lines including KRAS mutant SW480 cells. Triple treatment of erlotinib, dabrafenib and CK2 inhibition further reduced proliferative activity for some cell lines, but effect size was modest.

We tested use of PI3K inhibition and found this highly effective in all cell lines, reducing 3 day viability to below 55% of controls. Addition of dabrafenib to GDC0941 further reduced growth in HT29 and Colo205 but not Lim2405 cells. Further addition of CK2 inhibition to GDC0941 showed similar effectiveness to the addition of dabrafenib, but also was the most effective approach to lower the proliferation of KRAS mutant colon cancer SW480 cells.

Conclusions: Inhibition of PI3K is an effective approach for regulating growth of BRAF colon cancer and can be enhanced with addition of CK2 inhibition.

Tumor-biopsy stratification based on mTOR-pathway activity and functional mutations in the upstream gene PIK3CA and PTEN

Jean-François Laes[1] and Joachim Fluhrer[2]

[1] OncoDNA
[2] Genostics

Background: mTOR pathway is frequently activated in human cancers. The oncogene *PIK3CA* coding for the PI3K p110a subunit and the tumor suppressor gene *PTEN* lie upstream of the mTOR pathway. Activating mutations in *PIK3CA* or null mutations in *PTEN* and its loss of expression can lead to mTOR pathway activation. Certain mTOR and PI3K inhibitors have been approved for the treatment of some cancer types, while others are under investigation.

Aim: To evaluate the relation between mTOR pathway activity and functional mutations in the upstream genes *PIK3CA* and *PTEN* in solid tumor biopsies.

Methods: 538 FFPE samples of 40 different cancer types were analyzed by IHC and NGS. mTOR pathway activation was identified by expression of the downstream effector p-4E-BP1. Activating *PIK3CA* mutations and null *PTEN* mutations were identified by NGS, and for *PTEN*, confirmed by IHC.

Results: mTOR pathway activation was identified in 83% of the samples. Moreover, 11%, 29% and 3% of the samples had mutations in *PIK3CA*, *PTEN* or in both, respectively. Overall, mTOR pathway activation was not significantly associated with the *PIK3CA* and *PTEN* genotypes. However, all samples with both *PIK3CA* and *PTEN* mutations displayed mTOR pathway activation ($\chi 2$ p=0.0471). Also, out of a total of 95 breast cancer samples, there were 5 samples that did not have mTOR pathway activation, and all (100%) of these had *PIK3CA* and *PTEN* mutations compared to 57% of breast cancer samples with mTOR pathway activation ($\chi 2$ p=0.0134). Finally, the percentage of *PIK3CA* mutations was higher in colorectal cancer samples with mTOR pathway activation (33%) than in colorectal cancer samples without mTOR pathway activation (14%; $\chi 2$ p=0.0484).

Conclusions: Tumor biopsy analyses based on combined tests of mTOR pathway biomarkers (by combining NGS and IHC) could potentially provide treatment informative stratification for particular cancer types.

Moving towards an interactive cancer shared care plan solution

Mark Harris[1], Melvin Chin[2,3], Winston LIauw[4,5] and Jane Taggart[6]

[1] Centre for Primary Health Care & Equity, UNSW Sydney; Translational Cancer Research Network (TCRN), UNSW Sydney.
[2] UNSW Translational Cancer Network
[3] Prince of Wales Hospital
[4] UNSW Translational Cancer Research Network
[5] St George Hospital
[6] UNSW Centre for Primary Health Care and Equity

Background: Shared care between cancer specialists and GPs is an acceptable model of follow-up care for patients and clinicians. An interactive care plan could support this model of care.

Aim: To identify the options, challenges and solutions in implementing an interactive, cancer e-shared care plan.

Methods: A cancer shared care plan incorporating a treatment summary, goals, tasks, roles and responsibilities was developed through a literature search and consultations.

A workshop with key stakeholders identified the issues, gaps, requirements and options for sharing a care plan using existing technology. Issues were discussed during subsequent meetings with input from eHealth NSW. A preferred interactive share care model for a pilot was agreed.

Results: Options for sharing the care plan included the use of My Health Record (MHR), HealtheNet and Sharepoint, a web-based collaborative platform. None of these options were integrated with ARIA or general practice systems.

Sharepoint met more of the identified requirements for sharing and collaboration than the other options, however, there are issues that will need to be addressed. For example, the sharing of clinical information with GPs who are external to the Local Health District is not advocated, the need for clinicians to log into the system will be a barrier to use and additional time will be required to set up access permissions at the patient level.

MHR did not support the uploading of the care plan and a work-around solution ended with all the formatting being lost. MHR could be used to view diagnostic and pathology results.

HealtheNet could provide access to the care plan and securely send it to GPs.

Conclusion: Cancer specialists and GPs are ready to share cancer follow-up of mutual patients but there are no available IT systems or governance frameworks to enable this. A facilitated model is required to test specialist-GP interactions.

Role of constitutive androstane receptor (CAR) in the regulation of liver cancer stem cells

Kyung-Jin Kim[1], Jacob George[2] and Liang Qiao[1]

[1] Storr Liver Centre, Westmead Institute for Medical Research (WIMR), the University of Sydney and Westmead Hospital, Westmead, NSW 2145, Australia
[2] Storr Liver Centre, Westmead Institute for Medical Research

Background: Liver cancer is a stem cell disease and liver cancer stem cells (LCSCs) are likely responsible for its initiation and treatment resistance. We have observed that constitutive androstane receptor (CAR) may play a critical role in human liver cancer and in particular in the regulation of LCSCs. Previous studies have revealed that CAR may play an oncogenic role in mice, but its role in human liver cancer is yet unclear. CAR was shown to regulate the biological function of human brain tumor stem cells, but its role in human LCSCs are unknown.

Aim: In this study, we aimed to investigate the possible role of CAR on LCSCs.

Methods: Expression of CAR and its downstream targets in human liver cancer tissues and LCSCs derived from PLC/PRF/5 cells were determined by qPCR. Statistical analysis was performed using student *t*-test.

Results: The expression of CAR is significantly reduced in human liver cancer tissues compared to matching non-cancerous hepatic tissues, and this was associated with a decreased expression of CAR downstream targets (including CYP2A6, CYP2B6, UGT1A1 and ABCG2). In the LCSCs derived from PLC/PRF/5, there was a significant decrease in CAR expression and this is associated with an increased expression of LCSCs markers (e.g., CD90, EpCAM, CD24, CD44, Oct4 and Sox2).

Conclusions: CAR may play a tumor suppressive role in human liver cancer and an important regulator for LCSCs. Further studies are under way to confirm the regulatory role of CAR on LCSCs and the underlying molecular mechanisms.

Systematic and Multi-Level of Consumer Engagement Model by Translational Cancer Research Network (TCRN)

Stella Jun[1], Gillian Begbie[2], Jeff Cuff[2], Kathryn Leaney[2], John Lewis[2], Peter Lewis[2], Ruth Lilian[2], Sue McCullough[2], Sue Suchy[2], David Synnott[2], Susan Taylor[2], Stephanie Macmillan[2] and David Goldstein[3]

[1] Translational Cancer research Network (TCRN)
[2] Translational Cancer Research Network
[3] UNSW Sydney

Background and context: The value of consumer engagement in cancer research projects is increasingly recognised by both researchers and funding bodies. In order to encourage widespread participation, many funding bodies now incorporate an evaluative component or metric for consumer involvement when allocating grants. However, researchers who are unfamiliar with this concept can struggle to access appropriate information and resources.

Aim: The TCRN aimed to develop a strategic model of consumer engagement in research that provides a more effective and systematic research support service to its members

Methods:

TCRN's in-house Consumer Advisory Panel (CAP) was developed. The TCRN has provided three levels of consumer services to its members. They are:

- Information workshop on the fundamentals of consumer engagement in research and successful cases to a wider group of researchers
- CAP group sessions for researchers looking for a broader consumer input
- 1:1 researcher-consumer partnerships for in-depth and ongoing consumer involvement

Outcomes:

Since its launch in 2012, the CAP has:

- Partnered and provided consumer input to over 75 research projects including TCRN flagships.
- Over 100 researchers have attended the Information sessions
- Engaged with 40 TCRN supported PhD students, connecting them to real-world outcomes and helping them effectively communicate their research from the earliest stages of their careers.
- In 2017, 3 major grants were awarded to TCRN members who have a CAP partner.

In the recent TCRN membership survey, consumer engagement was selected as one of the most valued research support services provided to its members.

Conclusions:

Through multi-level of consumer engagement activities, the TCRN has been effective in providing appropriate consumer support to its members and consequently has successfully promoted the concept of consumer engagement in cancer research.

The translational significance of this work is that the TCRN provides systematic research support to the researchers who, in turn, can develop effective and evidence-based research projects that with consumers' input.

SMG1 LOSS ENHANCES MTOR SIGNALLING IN CHRONIC LYMPHOCYTIC LEUKEMIA PATIENTS

Alexander James[1], Patricia Rebeiro[2], Uda Ho[3], Silvia Ling[4], Martin Lavin[3] and Tara Roberts[5]

[1] Ingham Institute for Applied Medical Research
[2] UNSW Sydney
[3] University of Queensland
[4] Liverpool Hospital
[5] Ingham Institute, Western Sydney University

Background: SMG1 is a member of the PI-3 kinase like kinase (PIKK) family of proteins which includes ATM, ATR, DNA-PK and mTOR. This family have well-characterised roles in responses to cellular stress including DNA damage and nutrient deprivation. SMG1 is central to nonsense-mediated decay (NMD), a process that degrades mRNA containing premature stop codons thus preventing the production of truncated proteins. NMD is particularly active in B and T cells to prevent expression of truncated B and T cell receptors consequently B and T cells have high SMG1 expression. In our mouse model loss of one SMG1 allele resulted in increased development of B cell cancers.

Aims: We aimed to understand how loss of SMG1 enhanced cancer cell growth and whether loss of SMG1 in patients alters their responses to therapy.

Methods: We combined the study of cell lines, animal models and patient cells to determine how loss of SMG1 dysregulated key signalling pathways.

Results: mTOR is the kinase core of two complexes: mTORC 1 and 2. Here we show that SMG1is a novel negative regulator of mTORC2. Immunoprecipitation experiments show that SMG1 interacts specifically with mTORC2 but not mTORC1. SMG1 knockdown in cell lines leads to increased activation of mTORC2 and increased phosphorylation of mTORC2 substrates Akt and Protein kinase C. In chronic lymphocytic leukaemia patients (CLL) >30% lacked detectable SMG1. Further, the level of SMG1 expression in CLL patients' B cells inversely correlated with Akt phosphorylation indicating that the loss of SMG1 increased mTORC2 signalling. Preliminary *ex vivo* assays suggest that CLL patient cells lacking SMG1 have altered susceptibility to mTOR inhibitor.

Conclusions: SMG1 interacts with the mTORC2 complex to negatively regulate its activity. SMG1 loss correlates with increased mTORC2 signalling in CLL patient cells and may identify a sub-group of patients with altered susceptibility to mTOR inhibition.

Targeting NAD+ biosynthesis as a therapeutic strategy for high-risk paediatric ALL

Klaartje Somers[1], Kathryn Evans[1], Leanna Cheung[1], Tara Pritchard[1], Mawar Karsa[1], Angelika Kosciolek[1], Shiloh Middlemiss[1], Lioubov Korotchkina[2], Olga Chernova[2], Andrei Gudkov[3], Murray Norris[4], Michelle Haber[4], Richard Lock[1] and Michelle Henderson[4]

[1] Children's Cancer Institute, Lowy Cancer Research Centre
[2] Oncotartis, Inc.
[3] Department of Cell Stress Biology, Roswell Park Cancer Institute
[4] Children's Cancer Institute

Background: The prognosis for children diagnosed with high-risk acute lymphoblastic leukaemia (ALL) is still dismal. More potent, selective and safer therapeutics are urgently needed. By performing a chemical library screen for compounds that preferentially target haematopoietic cancers, we identified a novel inhibitor of nicotinamide phosphoribosyltransferase (NAMPT), OT-82, that potently and selectively killed blood cancer cells.

Aim: We investigated the therapeutic potential of OT-82 for high-risk paediatric ALL by investigating its activity in a broad panel of systemic patient-derived xenograft models of the disease.

Methods: We determined the *in vivo* efficacy of OT-82 against a panel of high-risk and poor outcome paediatric patient-derived ALL xenograft models, comprising infant MLL-rearranged ALL (n=6), B-Cell Precursor ALL (n=9), including Philadelphia chromosome positive (Ph^+) and Ph-like ALL, as well as T-cell ALL (n=6) including early T cell precursor ALL. Response to treatment was assessed by event-free survival and stringent objective response criteria modeled after the clinical setting.

Results: OT-82 was well-tolerated and demonstrated impressive single agent *in vivo* activity, achieving significant leukaemia growth delay in 95% (20/21) and objective responses in 86% (18/21) of xenografts. Interestingly, for the particularly aggressive subtype of infant MLL-rearranged ALL, OT-82 alone had comparable efficacy to an induction-type therapeutic regimen combining three chemotherapeutics (vincristine, dexamethasone and L-asparaginase). OT-82 also enhanced the efficacy of chemotherapeutic drug cytarabine and targeted therapeutic Dasatinib, each used in the treatment of paediatric high-risk ALL. OT-82 depleted cellular NAD^+, decreased ATP levels and inhibited the NAD^+-requiring DNA damage repair enzyme PARP-1, culminating in apoptosis induction. Serum levels of extracellular NAMPT were decreased in mice treated with OT-82, indicating its potential as a pharmacodynamic marker for OT-82 action *in vivo*.

Conclusions: NAMPT inhibitor OT-82 is a promising novel therapeutic strategy for a broad spectrum of high-risk paediatric ALL cases for whom novel therapeutic options are urgently needed.

Inhibition of histone chaperone FACT potentiates chemotherapeutics for MLL-rearranged leukaemia

Klaartje Somers[1], Angelika Kosciolek[1], Ali El-Ayoubi[1], Angelika Bongers[1], Shiloh Middlemiss[1], Richard Lock[1], Andrei Gudkov[2], Katerina Gurova[2], Murray Norris[3], Michelle Haber[3] and Michelle Henderson[3]

[1] Children's Cancer Institute, Lowy Cancer Research Centre
[2] Department of Cell Stress Biology, Roswell Park Cancer Institute
[3] Children's Cancer Institute

Background: Survival rates for infants suffering from Mixed Lineage Leukaemia (*MLL*)-rearranged acute lymphoblastic leukaemia (MLL-r ALL), are particularly dismal. In addition, for those patients who survive, currently applied chemotherapeutic treatment protocols are associated with severe short-term and long-term health effects. More targeted therapies that are less toxic and allow for dose reduction of chemotherapeutic drugs are thus urgently needed.

CBL0137, a small molecule curaxin that inhibits the activity of the histone remodelling Facilitates Chromatin Transcription (FACT) complex, has demonstrated anti-cancer efficacy as a single agent and as a chemosensitising agent for DNA-damage inducing chemotherapeutics. The compound is currently in a phase I clinical trial for refractory adult cancers.

Aim: We aimed to investigate the potential of CBL0137 as a single agent and chemosensitiser for standard of care chemotherapeutics used in the treatment of paediatric MLL-r ALL.

Methods: We investigated the therapeutic potential of CBL0137 by testing its efficacy against MLL-r leukaemia cell lines and infant MLL-r ALL patient-derived xenografts *in vitro* and *in vivo*, as a single agent and in combination with currently used chemotherapeutics.

Results: CBL0137 affected the viability of MLL-r leukaemia cells *in vitro* with sub-micromolar IC50s by activating p53, inhibiting the NFκB pathway and inducing apoptosis. *In vivo*, treatment with CBL0137 (40-45 mg/kg, 2x week, 4 weeks, intravenous) induced leukaemia regressions as a single agent in all (5/5) tested MLL-r ALL PDX models. In addition, CBL0137 enhanced the therapeutic effects of an induction type chemotherapeutic combination of vincristine, dexamethasone and L-asparaginase as well as relapse chemotherapeutic cyclophosphamide in a MLL-r ALL PDX model *in vivo*.

Conclusions: CBL0137 showed single agent efficacy against infant MLL-r ALL and potentiated the therapeutic efficacy of currently used chemotherapeutics for the disease, indicating its therapeutic potential and supporting inclusion of the compound in novel clinical trials for infant leukaemia.

Developing a text message program to support women's health after breast cancer treatments

Anna Singleton[1], Stephanie R. Partridge[1,2], Kerry Sherman[3], Elisabeth Elder[4] and Julie Redfern[1,5]

[1] The University of Sydney, Faculty of Medicine and Health, Westmead Applied Research Centre (WARC), Westmead, NSW, Australia
[2] The University of Sydney, Faculty of Medicine and Health, Sydney School Public Health, Prevention Research Collaboration, Charles Perkins Centre, Camperdown, NSW, Australia
[3] Macquarie University, Centre for Emotional Health, Department of Psychology, Sydney, NSW, Australia
[4] Westmead Breast Cancer Institute, Westmead Hospital, Westmead, NSW, Australia
[5] The George Institute for Global Health, Camperdown, NSW, Australia

Background: Breast cancer is the leading cancer in women in Australia and worldwide. In recent years, the number of women surviving breast cancer has increased, prompting need for support during recovery and beyond. Text messaging programs offer a simple way to provide support to people with chronic disease. However, there is little evidence for the role of text messages in supporting women's recovery after breast cancer treatments.

Aim: To develop an evidence-based, engaging and appropriate text message program for women recovering from breast cancer treatments.

Methods: The text messages were developed using an established, mixed-methods process. First, key experts and consumer representatives participated in a workshop. Participants discussed the text message themes, the frequency and timing of message delivery and message personalisation. Participants then drafted text messages based on current evidence, guidelines and experience. Messages were collated and distributed to breast cancer experts and consumers to rank the appropriateness, usefulness and clarity on a 5-point Likert scale.

Results: Breast cancer experts (surgeon, researcher, clinical psychologist, physiotherapist and consumer representatives) attended the workshop (N=6). Participants agreed on four, main text message content themes: 1) physical activity/nutrition, 2) medication adherence, 3) social and emotional well-being, and 4) general health tips. Experts agreed on a one-way message delivery system, where messages will be sent four times per week, at random times and days, to increase engagement. The team drafted a total of ~300 messages, which were each reviewed by at least 3 experts and 3 consumers, resulting in a final message bank of ~200 evidence-based text messages.

Conclusions: We developed evidence-based text messages to support women's health after breast cancer treatments. We will test the effectiveness of the messages in a randomised controlled trial.

Translational significance: If the text message support program is effective, it can be easily scaled-up nationally and internationally.

Discovery of novel prognostic markers in triple-negative breast cancer by MALDI MS imaging

Robert Baxter[1] and Leo Phillips[1]

[1] University of Sydney, Kolling Institute, Royal North Shore Hospital

Background: In about 15% of breast cancer diagnoses the tumours are triple-negative (TNBC), i.e. negative for estrogen receptors (ER), progesterone receptors, and HER2 overexpression. Women with TNBC have relatively poor outcomes, with early relapse a common feature. By molecular and histopathological analysis TNBC overlaps ~80% with basal-like breast cancer. There are no widely-accepted biomarkers of outcome in these patients, and no targeted therapies with confirmed benefit.

Aim: To discover novel indicators of poor survival in TNBC.

Methods: We used MALDI mass spectrometry (MS) imaging of tryptic peptides to compare regions of cancer and benign tissue in 10 formalin-fixed, paraffin-embedded sections of TNBC tumours. Peptides that distinguished between cancer and benign tissue in at least 3 tumours with a ROC area-under-the-curve >0.7 were identified from a reference library constructed by LC-MALDI-MS/MS analysis of the same tissues.

Results: We found 14 proteins, all upregulated in TNBC tissue, for which identified peptides met these criteria. Using Kaplan-Meier analysis to examine the relationship between expression of genes encoding the corresponding proteins, and recurrent-free survival (RFS), we found that high expression of nine of these genes in basal-like TNBC tumours was associated with significantly worse RFS than low expression, most with hazard ratios >2. In contrast, in ER-positive tumours, high expression of these genes had low, or no, association with worse RFS. Initial STRING network analysis showed no obvious functional relationships except among collagen subunits COL1A1, COL1A2, and COL63A, but manually adding EGFR to the analysis revealed a network including 9 of the 14 proteins.

Conclusions: Among the discovered proteins, some (e.g. SOX11, COL1A2) have previously been considered as cancer biomarkers, while others (e.g. ZSWIM8, CCDC24) have no known function. These proteins are proposed as putative prognostic indicators of poor RFS in TNBC, and some may also be considered as possible targets for future therapies.

Overcoming Pgp-Mediated Drug-Resistance by Releasing Lysosomal Stored Doxorubicin with Lysosomal Targeting Agents

Lionel Leck[1], Nicole A. Seebacher[1], Des R. Richardson[1] and Patric J. Jansson[1]

[1] University of Sydney

Introduction: The intracellular distribution of chemotherapeutics has been known to cause variation in the activity and selectivity of drugs. Notably, cytotoxic chemotherapeutic of the drug, doxorubicin (DOX) caused by drug transporter (*e.g.* P-glycoprotein, Pgp) has been observed in various Pgp-expressing subtype cells.

Aims: This study aimed to investigate the synergistic effect and mechanism of the anti-cancer agents in drug resistant Pgp-expressing cells.

Methods: This study utilized different anti-cancer agents as well as inhibiting Pgp to elucidate the synergistic effect and mechanism of these drugs in KB31 and KBV1 cervical carcinoma, MCF7 and MDA-MB-231 breast cancer, and HCT-15 colorectal adenocarcinoma cancer cell lines.

Results: This studies demonstrated the synergistic effect between di-2-pyridylketone 4,4-dimethyl-3-thiosemicarbazone (Dp44mT), or di-2-pyridylketone 4-cyclohexyl-4-methyl-3-thiosemicarbazone (DpC) with DOX. Herein, we demonstrated that both DpC and Dp44mT effectively kills Pgp expressing cancer cells, whereas DOX potently destroys non-Pgp-expressing tumour cells. The underlying mechanism involves both drugs being transported into the lysosomes through the transport activity of Pgp, where they have shown to stimulate the lysosomal-membrane permeabilization to release DOX trapped within the lysosomes. This novel approach of loading intracellular lysosomes with DOX, and subsequent permeabilization with DpC or Dp44mT causes the re-localization of DOX within the 'safe house' of the lysosomes to its nuclear target, where it can carry out its activity by enhancing cytotoxicity against resistant tumour cells. Indeed, the synergistic interaction between these agents can be prevented through the use of 1) pharmacological inhibitors, Elacridar; 2) Pgp silencing or; 3) lysosomal-membrane stabilization to inhibit the re-localization of DOX from lysosomes to the nucleus.

Conclusion: This novel strategy and potent anti-tumour efficacy observed between the thiosemicarbazones and DOX offers a promising avenue for future research and in the development of effective therapeutic treatments designed to treat advanced and resistant heterogeneous tumours in terms of P-gp expression.

Community-based allied-health professionals in the provision of cancer care: a cross sectional survey

Chris TZAR[1], Chis TZAR[2], Kerry TILLER[3], Gnana SPAILE[4], Taylor JONAS[5], Sue SUCHY[6], Stella JUN[7] and Mark HARRIS[8]

[1] (UNSW Medicine) LIFESTYLE CLINIC
[2] University of NSW
[3] Prince of Wales Hospital, RANDWICK NSW
[4] Prince of Wales Hospital, RANDWICK NSW; Sydney Children's Hospital, RANDWICK NSW
[5] Prince of Wales Hospital, RANDWICK NSW
[6] Prince of Wales Hospital, RANDWICK NSW; Translational Cancer Research Network (TCRN)
[7] Translational Cancer research Network (TCRN)
[8] Centre for Primary Health Care & Equity, UNSW Sydney; Translational Cancer Research Network (TCRN), UNSW Sydney.

Background: While the incidence of cancer in Australia is increasing, survival rates have also improved. Cancer survivors often need long-term health care by a wide range of practitioners including allied health professionals in the community. Therefore, there is a need to explore allied health professionals' interest, education and confidence level in providing care and treatment for cancer survivors.

Aims: To identify the interest, skills and experience of community-based allied health professionals who care for people diagnosed with cancer and to develop education opportunities for allied health professionals to facilitate best practice support.

Methods: An online survey of community-based allied health professionals will ask participants to self-assess their interest, skills and experience in providing care for people who have been diagnosed with cancer. The survey tool was developed and reviewed by experts in cancer survivorship care including psychologists, physiotherapists, exercise therapists, dental surgeons, GPs and a consumer for professional and cultural competency. This survey will be distributed using the mailing list from the *Central and Eastern Sydney Allied Health Network* (CESAHN) and the *Central and Eastern Sydney Primary Health Network* (CESPHN). An in-house list of allied health professionals will also be used to access allied health professionals who are not members of those networks. Qualtrics software will be used to collect data and data analysis will include descriptive statistics and comparison between different groups of allied health professionals and the location of their practice (based on Local Government Area).

Results: Preliminary results will be presented at the conference

Conclusion: Findings will be used to design and develop training and educational activities for allied health professionals. The translational significance of this research is that it will result in meaningful health outcomes by ensuring the cancer care accessed by survivors is provided by professionals in the community who can provide gold standard evidence-based services.

A critical review of instruments to measure cancer-related cognitive changes (CRCC) in women with breast cancer

Lynette Mackenzie[1], Hannah Nunn[1] and Joanne Lewis[1]

[1] University of Sydney

Background: Cancer-related cognitive changes (CRCC) are recognised as a potential late effect following cancer diagnosis and treatment. However, its presentation may be difficult to assess as it can sometimes be a mild deficit.

Aims: The purpose of this critical review was to determine what assessment instruments are available for clinicians to identify CRCC in women with breast cancer, and to determine the psychometric properties of these assessment tools.

Methods: A critical review design was undertaken following PRISMA guidelines. Searches were conducted in the following databases: MEDline, CINAHL, Web of Science Core Collections, OT Seeker, Scopus and PsychInfo. Selected articles were appraised using a standardised evaluation form. Each identified assessment tool was further evaluated according to its psychometric properties, and data were independently extracted from the selected articles by two researchers. An extension of a scoping review (originally conducted in February 2013) was performed to identify potential instruments. Searches were completed in eight databases to: (a) identify any new literature from January 2013 to December 2017, (b) identify instruments that may have clinical utility for practitioners and (c) extract evidence about the psychometric properties of the identified measures. Critical analysis of both the studies and the instruments identified within the studies were undertaken in order to assess the quality of the instruments.

Results: Twenty-three studies were identified, with a total of 20 assessment instruments potentially available for use with the breast cancer population. Four instruments were identified as having the strongest psychometric properties and potential clinical utility.

Conclusion: Results indicate a lack of information about psychometric properties when selecting an instrument for the assessment of CRCC in research studies. This has an impact on the ability of clinicians to identify issues relating to CRCC in a standardised way, impeding the development of evidence-based care plans for individuals recovering from breast cancer.

Annexin A6 modulates the sensitivity of EGFR overexpressing cells towards EGFR tyrosine kinase inhibitors

Yasmin Elmaghrabi[1], Monira Hoque[1], Paul Timpson[2], Carles Rentero[3], Carlos Enrich[3] and Thomas Grewal[1]

[1] School of Pharmacy, University of Sydney, Sydney, NSW 2006, Australia.
[2] Garvan Institute of Medical Research
[3] Departament de Biomedicina, Unitat de Biologia Cel·lular, Centre de Recerca Biomèdica CELLEX, IDIBAPS, Facultat de Medicina i Ciències de la Salut, Universitat de Barcelona, Spain.

Background: Inhibition of epidermal growth factor receptor (EGFR) signalling with tyrosine kinase inhibitors (TKIs) is a potent approach to inhibit cancer growth and progression. However, the sensitivity of cancer cells towards TKIs is often compromised by EGFR mutations or affected by other less-well understood mechanisms. The latter also involves the expression levels of scaffold proteins, which stabilize and establish the formation of multifactorial signaling complexes. This includes Annexin A6 (AnxA6), a member of the Ca^{2+}- and membrane binding annexins, which recruits negative regulators of EGFR and the Ras/MAPK pathway to the plasma membrane. In EGFR overexpressing A431 cells, a common model to study EGFR-related cancers, ectopic AnxA6 expression (A431-A6) promotes membrane targeting of p120GAP to inhibit Ras activity, and stimulates PKCα-mediated T654-EGFR phosphorylation. Reduced EGFR and Ras activation in A431-A6 cells correlates with reduced growth, migration and invasion (Koese et al., Oncogene 32: 2858-72, 2013; Vilá de Muga et al., Oncogene 28: 363-77, 2009).

Aim: Here, we analyzed the potential of AnxA6 to increase the sensitivity of EGFR overexpressing cells towards EGFR tyrosine kinase inhibitors.

Methods: A431-WT and A431-A6 cell growth (± EGFR-TKIs: gefitinib, erlotinib) was determined in colony formation, MTS, and spheroid growth assays. For cell migration, wound healing assays (± EGFR-TKIs: gefitinib, erlotinib) were performed. EGFR tyrosine and threonine phosphorylation in A431-WT, A431-A6 xenografts (± PKCα depletion) was analysed by western blotting.

Results: In A431-A6 xenografts, stable PKCα depletion increases tumor size, EGFR tyrosine phosphorylation and MAPK activity. Moreover, elevated AnxA6 levels correlate with increased ability of TKIs (gefitinib, erlotinib) to inhibit A431-A6 cell proliferation, spheroid growth and migration.

Conclusions: Altogether these findings implicate that modulation of expression levels of scaffold proteins like AnxA6 can contribute to alter the sensitivity of EGFR-related cancer cells towards TKIs.

Targeting the Metastasis Suppressor NDRG1 to Re-tune Oncogenic Cell Signaling Pathways in Pancreatic Cancer.

Zaklina Kovacevic[1], Sharleen Menezes[1], Leyla Fouani[1], Michael L. H. Huang[1] and Des Richardson[1]

[1] University of Sydney

Background: Pancreatic cancer (PaCa) is a highly aggressive disease with a mortality rate >95%. Current therapeutics for PaCa are failing due to the development of resistance and high metastatic propensity. The metastasis suppressor N-myc down-stream regulated gene 1 (NDRG1) can potently inhibit PaCa progression and metastasis and presents a promising new molecular target for this disease.

Aim: We aimed to elucidate molecular mechanisms of NDRG1 function in PaCa and how we can utilize this protein as a novel therapeutic target to inhibit PaCa progression and metastasis. We developed a novel class of thiosemicarbazone anti-cancer agents that up-regulate NDRG1 and also assessed their efficacy against PaCa *in vitro* and *in vivo*.

Methods: We examined key oncogenic signaling pathways that drive PaCa, including EGFR, NF-κB, TGF-β, *etc.* and their major down-stream targets (PI3K/AKT, MAPK, SMADs, ZEB-1) to elucidate how NDRG1, and novel agents targeting this molecule, inhibit the epithelial to mesenchymal transition (EMT) and subsequent PaCa metastasis.

Results/Conclusions: We discovered that NDRG1 plays a major, central role in inhibiting multiple oncogenic signaling pathways that drive PaCa progression and metastasis. NDRG1 inhibited activation and down-stream signaling of the EGFR family of receptor tyrosine kinases. Further, the TGF-β signaling pathway was re-tuned to activate tumour suppressive rather than oncogenic signaling. NDRG1 also inhibited major drivers of the EMT, including SNAIL, SLUG and ZEB, while promoting membrane expression of the cell adhesion molecules E-cadherin and β-catenin. These latter effects were mediated by inhibition of NF-κB signaling.

Importantly, the novel thiosemicarbazones up-regulated NDRG1 and inhibited PaCa oncogenic signaling *in vitro* and *in vivo*. These agents also potently inhibited PaCa tumour growth *in vivo*, being more effective than the currently used agent, gemcitabine. Hence, targeting NDRG1 using these agents may provide an effective new strategy for re-tuning oncogenic signaling and inhibiting metastatic progression of PaCa.

NUCLEAR IGFBP-3 IS A POTENTIAL BIOMARKER FOR RESPONSE TO EGFR-SPHINGOSINE KINASE TARGETED THERAPY IN TNBC.

Sohel Julovi[1], Janet Martin[1] and Robert Baxter[1]

[1] University of Sydney, Kolling Institute, Royal North Shore Hospital

Background: Triple-negative breast cancer (TNBC) has no approved targeted therapy and is commonly treated with adjuvant chemotherapy such as doxorubicin. An oncogenic pathway involving sphingosine kinase-1 (SphK1) and epidermal growth factor receptor (EGFR) is initiated in TNBC cell lines *in vitro* by insulin-like growth factor binding protein-3 (IGFBP-3), which is highly expressed in basal-like TNBC and prognostic for poor recurrence-free survival. In combination, inhibitors of EGFR (gefitinib) and SphK (fingolimod) induce a strongly synergistic cytostatic effect in TNBC cell lines, which is prevented *in vitro* by IGFBP-3 downregulation. Therefore we evaluated IGFBP-3 as a response biomarker in TNBC tumours after treatment with the inhibitor combination, with or without doxorubicin.

Methods: Tumours were established in mice from human basal-like TNBC cell lines HCC1806 and MDA-MB-468, and treated with fingolimod plus gefitinib (F+G) ± doxorubicin (2 mg/kg/week, the maximum tolerated dose). Tumours were analysed by IHC, and cell proliferation *in vitro* was monitored by live-cell imaging.

Results: *In vitro*, F+G acted synergistically with doxorubicin to markedly inhibit proliferation. *In vivo*, F+G significantly inhibited tumour growth and enhanced mouse survival, but doxorubicin had minimal effect alone, and no significant incremental effect with F+G. Tumour IGFBP-3 staining was predominantly nuclear, was positively correlated with Ki67, and was significantly downregulated by F+G, with no added doxorubicin effect. High nuclear IGFBP-3 IHC scores were strongly associated with worse mouse survival, while high apoptosis (cleaved caspase-3) scores were associated with better survival.

Conclusions: The F+G combination alone is highly inhibitory to basal-like TNBC tumour growth but synergism with doxorubicin was not seen *in vivo*, possibly because of dose-limiting doxorubicin toxicity. Nuclear IGFBP-3 staining may have utility as a biomarker of treatment response in TNBC, alone or together with Ki67 and cleaved caspase-3. Supported by Cancer Council NSW.

ROBO2 is a stroma suppressor gene in the pancreas through regulation of TGF-beta

Andreia Pinho[1], Mathias Van Bulck[2], Lorraine Chantrill[3], Mehreen Arshi[4], David Herrmann[4], David Gallego-Ortega[4], Anthony Gill[5], Andrew Biankin[6], Jianmin Wu[7], Paul Timpson[4] and Ilse Rooman[2]

[1] Garvan Institute of Medical Research and Macquarie University
[2] Oncology Research Centre, Vrije Universiteit Brussel
[3] St. Vincent's Hospital and Garvan Institute of Medical Research
[4] Garvan Institute of Medical Research
[5] University of Sydney and Garvan Institute of Medical Research
[6] University of Glasgow
[7] Peking University Cancer Hospital and Institute

Background: Pancreatic ductal adenocarcinoma (PDAC) has a dismal prognosis, being predicted to become the second leading cause of cancer-related death by 2030. Chronic pancreatitis is a risk factor for PDAC and both diseases are characterized by a strong desmoplastic response, comprised of activated myofibroblasts and immune cell infiltrates.

Aim: Whereas genomic aberrations in the SLIT-ROBO pathway are frequent in PDAC, their role in the pancreas is unclear. We have used an integrative approach combining the study of murine models and PDAC patients with the objective of unravelling the function of SLIT-ROBO signaling in pancreatic disease.

Methods: RNA expression was analysed in murine normal pancreas, pancreatitis and PDAC. Cell cultures and experimental pancreatitis were studied using pancreas-specific Robo2 ($Pdx1^{Cre}$;$Robo2^{F/F}$) and whole-body Slit1 ($Slit1^{-/-}$) knockout mice. Gene and protein expression were assessed in a cohort of PDAC patients (n=109).

Results: In mouse pancreatitis and PDAC, epithelial Robo2 expression is lost while Robo1 expression becomes most prominent in the stroma. $Pdx1^{Cre}$;$Robo2^{F/F}$ pancreatic cell cultures showed increased activation of Robo1-positive myofibroblasts and induction of TGF-β and Wnt pathways. Likewise, pancreatitis in $Pdx1^{Cre}$;$Robo2^{F/F}$ mice enhanced myofibroblast activation, collagen crosslinking, T-cell infiltration and tumorigenic immune markers. Similar results were obtained using $Slit1^{-/-}$ animals. Moreover, TGF-β inhibition using galunisertib treatment suppressed Robo2-mediated effects.

In patients, ROBO2 expression is overall low in PDAC while ROBO1 is variably expressed in epithelium and high in stroma. ROBO1 expression is correlated with markers of activated stroma, Wnt and TGF-β pathways. $ROBO2^{low}$;$ROBO1^{high}$ patients present the poorest survival.

Conclusions: Robo2 acts non-autonomously as a stroma suppressor gene by restraining myofibroblast activation and inflammation in the pancreas. ROBO1/2 expression is prognostic in PDAC patients and may guide therapy with TGF-β inhibitors or immune modulating agents, currently being tested in clinical trials for advanced pancreatic cancer.

Interaction of IGFBP-3 with NONO/SFPQ in the breast cancer response to DNA damaging chemotherapy

Hasanthi de Silva[1], Mike Lin[1], Leo Phillips[1], Janet Martin[1] and Robert Baxter[1]

[1] University of Sydney, Kolling Institute, Royal North Shore Hospital

Background: Women with triple-negative breast cancer (TNBC) are generally treated by chemotherapy but may develop chemoresistance by DNA double-strand break (DSB) repair. PARP inhibitors have been trialled to block DNA repair in these cancers. We previously reported that IGFBP-3 forms nuclear complexes with EGFR and DNA-dependent protein kinase (DNA-PKcs) to modulate DSB repair by non-homologous end-joining (NHEJ) in TNBC cells.

Aim: To discover new IGFBP-3 binding partners involved in chemoresistance through stimulation of DSB repair.

Methods: The IGFBP-3 interactome was analyzed by LC-MS/MS after coimmunoprecipitation. Protein interactions were confirmed in basal-like TNBC cell lines HCC1806 and MDA-MB-468 after 20 μM etoposide treatment by coimmunoprecipitation and proximity ligation assay. NHEJ activity was assessed by *in vitro* end-joining assays and DNA DSBs were measured by gamma-H2AX.

Results: In response to etoposide, the DNA/RNA binding protein, Non-POU domain-containing octamer-binding protein (NONO) and its dimerization partner Splicing factor, proline/glutamine-rich (SFPQ) formed complexes with IGFBP-3. These interactions were blocked by EGFR and DNA-PKcs inhibition, and by PARP inhibitors veliparib and olaparib, which also reduced DNA end-joining activity and caused gamma-H2AX accumulation. Downregulation of the long noncoding RNA in NHEJ pathway 1 (LINP1) also blocked IGFBP-3 interaction with NONO-SFPQ.

Conclusions: The findings suggest a PARP-dependent role for NONO and SFPQ in IGFBP-3-dependent DSB repair and the possible involvement of LINP1 in the complex formation. We propose that combination targeting of the DNA repair function of IGFBP-3 may enhance chemosensitivity in basal-like TNBC, thus improving patient outcomes.

Supported by National Breast Cancer Foundation, Australia.

Targeting the aryl-hydrocarbon receptor (AhR) pathway to selectively kill breast cancer cells

Jayne Gilbert[1], Jennifer Baker[2], Stefan Paula[3], Adam McCluskey[2] and Jennette Sakoff[4,5,6]

[1] Calvary Mater Newcastle Hospital, Edith St, Waratah NSW, Australia
[2] University of Newcastle, Callaghan NSW, Australia
[3] Perdue University, Indiana, USA
[4] Dept. of Medical Oncology, Calvary Mater Newcastle Hospital, NSW 2298 Australia
[5] Hunter Cancer Research Alliance (HCRA), Newcastle, NSW, Australia
[6] University of Newcastle, Callaghan, NSW 2308 Australia

Background: We have identified a class of small molecule naphthalamides that selectively kill breast cancer cells grown in culture whilst having little to no effect on cells derived from other tumour types. Our lead compound NAP-6 is up to 300 - fold more potent at inhibiting the growth of breast cancer cell lines (MCF7, BT474, T47D, ZR-75-1, SKBR3 and MDAMB468) than normal breast cells (MCF10A). Furthermore, NAP-6 remains active in the MCF7/VP16 cell line which overexpresses the drug resistance ABCC1 gene.

Aim: The aim of this study is to determine the mechanism-of-action of NAP-6.

Methods: The MTT growth inhibition assay, cell cycle analysis, morphologic assessment, western blotting, enzyme inhibition, dual luciferase reporter assay for the xenobiotic response element (XRE), siRNA, qRT-PCR, and modelling were used to characterise the effect of NAP-6 in breast cancer cell line models.

Results: We show that NAP-6 induces DNA damage, checkpoint activation, S-phase cell cycle arrest, and cell death in the triple negative breast cancer cell line MDA-MB-468. Importantly, we show that NAP-6 mediates its effects via the Arylhydrocarbon (AhR) receptor pathway, a pathway known to be active in breast cancer. Specifically, NAP-6 activates the AhR which promotes nuclear translocation, binding to the XRE, and induction of the CYP1 family of metabolising enzymes. Within hours CYP1A1, CYP1A2 and CYP1B1 are induced 250, 18 and 6-fold, respectively. Small molecule antagonism of AhR and CYP1 together with siRNA knockdown of AhR ameliorates the effects of NAP-6 and its metabolic conversion to a reactive DNA targeting molecule. Molecular modelling of NAP-6 demonstrates unique binding pockets in the AhR.

Conclusions: We have shown that NAP-6 targets breast cancer via the AhR pathway and identify this pathway as a potential target for the treatment of breast cancer.

Translational Research Aspect: This study represents the translation of knowledge from T1 to T2.

Can risk attitudes determine sun-exposure behaviours and modify a melanoma genomic risk intervention?

Rachael Morton[1], Rebecca Asher[1], Edward Peyton[1], Anh Tran[1], Amelia Smit[2], Phyllis Butow[3], Michael Kimlin[4], Suzanne Dobbinson[5], Sarah Wordsworth[6], Louise Keogh[7] and Anne Cust[8,9]

[1] NHMRC Clinical Trials Centre, The University of Sydney
[2] The University of Sydney
[3] Psycho-oncology Co-operative Research Group, School of Psychology, The University of Sydney, NSW, Australia
[4] Cancer Council Queensland
[5] Cancer Council Victoria
[6] The University of Oxford
[7] The University of Melbourne
[8] Cancer Epidemiology and Prevention Research, Sydney School of Public Health, The University of Sydney, NSW, Australia
[9] Melanoma Institute Australia, The University of Sydney, NSW, Australia

Background: Preventing melanoma by reducing exposure to ultra-violet radiation from sunlight is difficult to achieve at a population level. Knowledge of personal genomic risk may motivate changes in sun-exposure, however it is unclear whether an individual's underlying propensity to take risks, influences subsequent behaviour change.

Methods: An Australian randomised trial with baseline data for 119 participants, evaluated the effect of providing personalised genomic information for melanoma risk, versus usual care, on sun-related behaviours. We measured domain-specific risk-taking (DOSPERT) in Health and Social domains at baseline, and classified participants as risk-seeking, risk-neutral or risk-averse. One-way ANOVA determined the association between socio-demographic characteristics and risk-taking score, and multivariable linear regression ascertained impact of an individual's underlying risk propensity on an objective measure of sun-exposure, standard erythemal dose (SED), at 3-months follow-up.

Results: Participants mean age was 53 years; 87% had a personal/family history of cancer; 19% were classified risk-seeking, 57% risk-neutral and 24% risk-averse for the Health domain, similar for the Social domain. The mean Health risk-taking score was significantly higher in younger participants (≤50 years: 13.86 vs. >50 years: 11.11, p=0.003); and lower in those with a personal/family history of skin cancer versus without (10.55 vs 13.33, p=0.009). Risk averse individuals had lower weekly mean SEDs at 3-months than risk neutral and risk seeking individuals (2.56, 5.81, 4.81 respectively, p=0.01). Risk seekers showed fewer sun protective habits (p<0.001); and higher intentional tanning, (p=0.01). At 3-months, risk seekers attained 16%-54% lower SEDs in the genomic information group compared with controls, however this was not significantly different across risk groups (interaction p=0.13).

Conclusion: Our study suggests an individual's underlying risk attitude is associated with sun-exposure behaviours, and may modify the effect of a genomic risk information behaviour change intervention. Young people without a history of skin cancer, and risk seekers may benefit most.

False positive results and incidental findings with CT or PET/CT surveillance in stage III melanoma patients

Amanda Nijhuis[1], Mbathio Dieng[2,3], Sally Lord[4], Jo Dalton[1], Alexander Menzies[1], Robin Turner[5], Jay Allen[1], Robyn Saw[1], Omgo Nieweg[1], John Thompson[1] and Rachael Morton[4]

[1] Melanoma Institute Australia
[2] NHMRC Clinical Trial Centre, The University of Sydney, NSW, Australia
[3] Cancer Epidemiology and Prevention Research, Sydney School of Public Health, The University of Sydney, NSW, Australia
[4] NHMRC Clinical Trials Centre, The University of Sydney
[5] University of Otago

Background: The use of surveillance imaging in melanoma follow-up is increasing. This study aimed to quantify false-positive and incidental findings from annual surveillance imaging in resected, asymptomatic, stage III patients.

Methods: Cohort study of patients treated at Melanoma Institute Australia (2000-2015) with baseline CT or PET/CT imaging and at least two annual surveillance scans. False-positives were defined as findings suspicious for melanoma recurrence that were not melanoma, confirmed by histopathology, subsequent imaging or clinical follow-up. Incidental findings were defined as not melanoma-related findings requiring further action. The outcomes of incidental findings were classified into three categories: 'benign', if they resolved spontaneously or were not seriously harmful; 'malignant' if a second malignancy was found; or 'other' if they were otherwise potentially harmful.

Results: Among 154 patients, 1022 scans were performed (154 baseline staging, 868surveillance) during a median follow-up of 85 months (IQR 64-115). On surveillance imaging, 77 false-positive results and incidental findings were identified in 61 of 154 patients (40%) on 69 of the 868 scans (8%). The frequency of these findings was 5-14% per year. An additional 181 investigations, procedures and referrals were performed to investigate them. The diagnosis was benign in 64 of 77 (88%) findings. Ten patients with a benign finding (6% of the cohort) underwent an unnecessary invasive procedure.

Conclusion: False-positive results and incidental findings are reported in almost half of all asymptomatic stage III melanoma patients undergoing annual surveillance imaging and the additional healthcare use is substantial. The risk of these findings persists over time. Clinicians need to be aware of the potential for false-positive and incidental findings resulting from surveillance imaging and discuss these risks with their patients.

Expression of lncRNAs in ovarian cancer-associated fibroblasts is prognostic for patient survival

Emily Colvin[1,2], Fatemeh Vafaee[3], Samuel Mok[4], Viive Howell[1,2] and Goli Samimi[5]

[1] Bill Walsh Translational Cancer Research Laboratory, Kolling Institute, Northern Sydney Local Health District, St Leonards, NSW 2065, Australia
[2] Northern Clinical School, Faculty of Medicine and Health, University of Sydney, Sydney, NSW 2006, Australia
[3] School of Biotechnology and Biomolecular Sciences, University of New South Wales, Sydney, NSW 2052, Australia
[4] Department of Gynecologic Oncology and Reproductive Medicine Research, Division of Surgery, The University of Texas MD Anderson Cancer Center, Houston, TX, USA
[5] Division of Cancer Prevention, National Cancer Institute, National Institutes of Health, Bethesda, MD, United States

Background: The tumour microenvironment is essential for the growth and metastasis of many solid tumours, including ovarian cancer. Cancer-associated fibroblasts (CAFs) represent the most abundant cell type in the tumour microenvironment and are responsible for producing the desmoplastic reaction that is a poor prognostic factor in ovarian cancer. Long non-coding RNAs (lncRNAs) have been shown to play important roles in several diseases, including cancer. However, very little is known about the role of lncRNAs in the tumour microenvironment.

Aim: To identify CAF-derived lncRNAs whose expression profiles are associated with patient survival and use computational approaches to predict their function.

Methods: CAFs were microdissected from 67 ovarian tumours and RNA extracted. Gene expression was analysed using Affymetrix U133 Plus 2.0 Arrays. Kaplan Meier/log-rank analysis was used to assess the association between expression of each lncRNA and patients' overall survival. Multivariate cox regression analysis was used to determine if differential expression of lncRNAs were independent predictors of survival. A network based 'guilt-by-association' approach was used to predict the function of lncRNAs associated with patient survival.

Results: Upregulation of 9 lncRNAs and downregulation of 1 lncRNA in ovarian CAFs were associated with poorer overall survival. Expression of 5 lncRNAs as well as response to chemotherapy and debulking status were significant by univariate analysis. To adjust for collinearity of the 5 lncRNAs, the first two principal components as well as response to chemotherapy and debulking status were incorporated into a multivariate model. The first principal component (HR=0.76, P=0.003), response to chemotherapy (HR=2.04, P=0.04) and debulking status (HR=0.27, P=0.03) were found to be independent predictors of survival. Functional enrichment analysis revealed these lncRNAs are likely to play roles in extracellular matrix organisation, immune response, autophagy and cell metabolism.

Conclusions: We have identified several CAF-derived lncRNAs whose expression levels are associated with survival, raising the likelihood that they play an important role in the tumour-promoting functions of CAFs. A greater understanding of how CAFs are regulated is essential in designing novel therapies targeting the tumour microenvironment.

Impact of Full-Field Digital Mammography versus Film-Screen Mammography: Systematic Review

Rachel Farber[1], Katy Bell[1], Nehmat Houssami[2], Kevin McGeechan[1], Sally Wortley[1], Michael Marinovich[1] and Alexandra Barratt[1]

[1] University of Sydney
[2] Sydney School of Public Health

Background: Most breast screening programs worldwide have replaced screen-film mammography with full-field digital mammography in expectation of technical, clinical and economic advantages. However, we are only now able to measure the effects of this practice shift on health outcomes among asymptomatic women eligible for population screening.

Aim: This systematic review aims to assess the impact of screening with digital mammography on screen detected breast cancer rates and interval cancer rates, as indicators of additional net benefit through early detection, or additional net harm from overdiagnosis.

Methods: We searched Medline, Premedline, PubMed, Embase, NHSEED, DARE and Cochrane databases and identified 2139 potentially eligible papers. 31 papers were included after exclusions for relevance, duplication and other exclusion criteria. Primary outcomes are detection rates and interval cancer rates. Secondary outcomes include recall rates, false positive rates, and positive predictive values. Results are stratified by first and subsequent screening rounds.

Results: Preliminary results for primary outcomes are available presently and reveal a small increase in screen detected cancers across all studies. In 7 studies with data on interval cancer rates, we observed a statistically non-significant decrease in interval cancer rates. Final data for primary outcomes and secondary outcomes will be presented at the conference.

Conclusion: Overall there has been a small increase in screen-detected cancers with the transition from film to digital mammography screening. The effect of this practice shift on interval cancers remains unclear. This observed pattern of results shows a small increase in cancer detection which may result in future benefit for screened women, but is also consistent with an increase in overdiagnosis. These results reinforce the need to carefully evaluate effects of future changes in technology such as 3D mammography to ensure incremental changes to screening programs do not lead to a poorer ratio of benefit to harm from screening.

The F98 rat orthotopic brain tumour resembles human poor prognosis glioblastoma

Naga Mutyala[1], Vibeke Catts[1], Susan Corley[1] and Louise Lutze-Mann[1]

[1] UNSW

Introduction: Glioblastoma (GBM) is the most common and lethal primary brain tumour in adults. The standard treatment plan comprises surgical resection, combined radiotherapy and temozolomide-based (TM) chemotherapy. Despite this intense multimodality therapy, the prognosis remains poor with the median survival rate less than 15 months. Therefore, improved therapies to treat this disease are urgently required. To evaluate the efficiency of novel agents and prioritise them for clinical trials, laboratory-based animal models that recapitulate the histology and molecular/genetic alterations of human GBM are critical.

Aims:

1. To investigate gene expression in an F98 rat GBM tumour model and identify whether it correlates with human GBM gene expression patterns.

2. To investigate the effect of olanzapine (OL), temozolomide (TM) and combination therapy (OL+TM=OLTM) on animal survival and gene expression changes in the F98 rat GBM tumour model.

Methods:

F98 rat GBM cells transfected with luciferase gene were implanted in the right cerebral hemisphere of Fischer rats. Treatment with OL, TM and OLTM commenced following confirmation of successful tumour implantation using bioluminescence. Tumour growth, body weight and animal survival were recorded. Messenger RNA levels in tumour and control brain tissue were determined using Affymetrix arrays and qRT-PCR.

Results:

F98 rat GBM tumours had a gene expression pattern similar to the poor prognosis human GBM, mesenchymal subtype. OLTM treatment down-regulated the pathways/genes promoting tumour progression, proliferation and invasion, with rats from this group surviving longer than all the other treatment groups.

Conclusion:

In terms of gene expression, F98 rat GBM has proved to have a significant correlation to an aggressive form of human GBM and therefore represents a rodent model for preclinical therapeutic studies. OLTM treatment showed modest potential as a novel treatment of GBM.

Targeting a novel metabolic regulatory mechanism in acute myeloid leukaemia

Patrick Connerty[1], Basit Salik[1], Jennifer Lynch[1] and Jenny Wang[1,2]

[1] Cancer and Stem Cell Biology Group, Children's Cancer Institute, Lowy Cancer Research Centre, University of New South Wales, Sydney, NSW 2052, Australia
[2] Centre for Childhood Cancer Research, Faculty of Medicine, University of New South Wales, Sydney, NSW 2052, Australia

Acute myeloid leukaemia (AML) is form of blood cancer which is frequently initiated by the transformation of healthy hematopoietic stem cells into leukemic stem cells (LSCs). Leukemic transformation and the development of LSCs are regulated by multiple mechanisms, including altered metabolic state and epigenetic processes. HOXA9 is a homeodomain transcription factor that induces the expansion of normal hematopoietic stem cells (HSCs) and is involved in the transformation of HSCs into LSCs producing AML. Aberrant HOXA9 expression is observed in approximately 50% of AML patient samples and is frequently associated with a poor prognosis. JMJD1C, a Jumonji C-Domain containing histone demethylase, has been reported to interact with the oncogenic transcription factor HOXA9. This interaction modulates the downstream genes essential for the function and growth of LSCs in AML. It remains unclear, however, how JMJD1C is involved in HOXA9-dependent transformation. This study reveals JMJD1C as a multifunctional protein with oncogenic roles largely determined by its interacting partners and cellular context.

Our results show that expression of JMJD1C in HOXA9-driven-pre LSC increased *in vivo* cell proliferation and tumorigenicity, counteracting adverse metabolic alterations and retaining the metabolic integrity of leukemic cells during tumorigenesis via modulation of cellular metabolism and upregulation. This suggests that JMJD1C sustains the bioenergetic requirements of HOXA9-dependent AML development. Pharmacologic inhibition of JMJD1C-mediated metabolism led to ATP depletion, necrosis/apoptosis and decreased tumor growth in leukemias co-expressing JMJD1C and HOXA9. Furthermore, anti-metabolic treatment effectively reduced leukemic burden in a highly translational AML patient-derived xenograft mouse model, indicating that targeting metabolic pathways in JMJD1C dependent AML could be a promising therapeutic approach in the treatment of the disease.

In conclusion, our findings report a novel role for oncoprotein JMJD1C in the regulation of cancer metabolism and identify a unique metabolic mechanism which can be explored therapeutically in AML.

Amiloride Provides Neuroprotection Against Preclinical Paclitaxel-Induced Peripheral Neuropathy

Munawwar Abdulla[1], Mallory Luke[1], Lital Livni[1], David Goldstein[2], Gila Moalem-Taylor[1] and Justin Lees[3]

[1] School of Medical Sciences, University of New South Wales, UNSW, Sydney, NSW, Australia, 2052.
[2] UNSW Sydney
[3] University of New South Wales

Background: Chemotherapy-induced peripheral neuropathy (CIPN) is a debilitating and dose-limiting side effect of many chemotherapy regimens and is a significant health issue for cancer survivors. Sensory symptoms include neuropathic pain, paraesthesia, and numbness which usually spread in a stocking and glove distribution. At present, there are no effective medications to treat or prevent CIPN, and the mechanisms by which symptoms are induced are principally unidentified. Paclitaxel (PTX) is a commonly used chemotherapeutic that induces peripheral neuropathy in a substantial proportion of patients.

Aim: To identify a clinically approved and effective neuroprotectant utilising *in vitro* and *in vivo* models of paclitaxel-induced peripheral neuropathy.

Methods: Primary mouse sensory neurons from 5-week-old C57BL/6 mice were cultured and treated with PTX to observe neurotoxic effects. Clinically approved drugs, which could be rapidly repurposed were assessed for their potential neuroprotective effects in culture. A physiologically relevant chronic CIPN model with 6 injections of PTX over a two-week period was established in C57BL/6 mice. The best candidate neuroprotectant from *in vitro* culturing was assessed for neuroprotective properties in the *in vivo* model.

Results: Paclitaxel caused significant reduction of axonal outgrowth from sensory neurons in culture and this effect was significantly alleviated by amiloride. PTX-treated mice developed mechanical allodynia and increased glial cell activation in the spinal cord. Amiloride given at 5 mg/kg, 2 hrs before each PTX treatment was found to have a significant effect in ameliorating mechanical allodynia and reducing astrogliosis in the spinal cord.

Conclusions: Taken together, *in vitro* and *in vivo* models provide evidence of amiloride's potential use to treat PTX-induced peripheral neuropathy. Furthermore, amiloride has previously been shown to have substantial anti-tumor activity, and therefore is a strong candidate for clinical testing.

Delta40p53 is associated with stem cell markers in breast cancer

Brianna Morten[1,2], Rodney Scott[1,2,3] and Kelly Avery-Kiejda[1,2]

[1] Priority Research Centre for Cancer Research, Innovation and Translation, School of Biomedical Sciences and Pharmacy, Faculty of Health and Medicine, University of Newcastle, NSW, Australia.
[2] Hunter Cancer Research Alliance, and Cancer research program, Hunter Medical Research Institute, NSW, Australia.
[3] Pathology North, John Hunter Hospital, New Lambton Heights, NSW, Australia.

Background: Breast cancer is the most common malignancy in women. p53 is essential in the maintenance of genomic stability and in the maintenance and regulation of cancer stem cells. The mutation frequency (~25%) of p53 in breast cancer is less than expected for a protein that plays a pivotal role in maintaining genomic integrity, suggesting that p53 is inactivated by mechanisms other than mutation. We have shown that the p53 isoform, Δ40p53, is abundantly expressed in breast cancer. Furthermore, a high Δ40p53:p53 ratio is associated with worse disease-free survival, indicating that disruption of p53 function by Δ40p53 may contribute to a more aggressive phenotype. However, its role in regulating breast cancer stem cells is unknown.

Aim: To establish the association of Δ40p53 with breast cancer stem cell markers and response to chemotherapy.

Methods: Gene expression arrays were performed on 64 breast cancers and differentially expressed genes were identified. MCF-7 breast cancer cells that stably overexpress Δ40p53 were treated with different chemotherapy agents; and examined for apoptosis as well as the expression of key targets by qPCR and immunofluorescence.

Results: Differentially expressed genes were identified between breast cancers with high and low Δ40p53 expression. These genes significantly enriched for pathways in stem cell regulation. Additionally, MCF-7 cells overexpressing Δ40p53 showed significant upregulation of pluripotent markers Nanog, Oct4 and Sox2 compared to controls. Following treatment with doxorubicin, Δ40p53-overexpressing cells showed a reduction in pro-apoptotic genes and decreased apoptosis, suggesting that high Δ40p53 expression in breast cancer can modulate the DNA-damage response.

Conclusion: This suggests that Δ40p53 may play a role in the regulation of breast cancer stem cells and this may be essential for modulating the DNA-damage response in these cells. Further studies are needed to assess if high Δ40p53 expression can alter the functionality of breast cancer stem cells.

Circulating cytokines predict toxicity in melanoma patients receiving combination immunotherapy

Esther Lim[1,2], Jenny Lee[3], Alexander Menzies[2], Matteo Carlino[2], Alexander Guminski[2], Kazi Nahar[2], David Palmieri[2], Edmond Breen[1], Richard Kefford[1,2], Richard Scolyer[2], Georgina Long[2] and Helen Rizos[3]

[1] Macquarie University
[2] Melanoma Institute Australia
[3] Biomedical Sciences, Faculty of Medicine and Health Sciences, Macquarie University, Sydney, NSW, Australia

Background: Combination anti-PD-1 and anti-CTLA-4 immunotherapy improves response rate of advanced melanoma patients compared to anti-PD-1 alone, but at the expense of greater toxicity. While efforts have been made to identify biomarkers to predict treatment response, there are no biomarkers to predict immunotherapy toxicity. **Aim**: We profiled plasma cytokine expression in melanoma patients receiving combination immunotherapy to identify biomarkers of toxicity.

Methods: Expression of 65 cytokines in 198 plasma samples from 100 melanoma patients (discovery cohort, 51 patients; validation cohort, 49 patients) receiving combination anti-PD-1 and anti-CTLA-4 was measured at baseline (PRE) and early during treatment (EDT, week 1-3) using the Luminex multiplex assay. Cytokine expression was correlated with immune-related toxicity, defined as toxicity that warranted discontinuation of treatment and administration of high dose steroids (≥50mg/day prednisolone equivalent), within 6 months of starting treatment.

Results: The median expression of all 65 cytokines was significantly higher in patients with toxicity compared to patients with no toxicity, at baseline and EDT, in the discovery (PRE; $p=0.01$, EDT; $p<0.01$) and validation cohorts (PRE; $p=0.03$, EDT; $p=0.02$). In addition, the median expression of six pro-inflammatory cytokines commonly associated with autoimmune disease (IFNg, IL-2, IL-17A, IL-1a, IL-1b and VEGF) was significantly higher at baseline and EDT in patients with toxicity ($p<0.01$ in the discovery, $p<0.05$ in the validation cohorts). Notably, VEGF was significantly elevated in patients with toxicity at baseline and EDT in both the discovery and validation cohorts.

Conclusion: Elevated levels of cytokines at baseline and EDT predicted development of immune-related toxicity. Pre-treatment measurement of circulating cytokines may have an important role in treatment selection for metastatic melanoma patients.

Translational significance: This work provides the first evidence that circulating cytokines can be used to predict toxicity onset, and is clinically important in pre-empting patients who would require intervention with immunomodulatory agents.

Novel patient-derived cell lines of squamous cell carcinoma: fidelity for preclinical modelling

Jay Perry[1], Bruce Ashford[1], Maely Gauthier[2], Ruta Gupta[3], Elahe Minaei[1], Gopal Iyer[4], Jonathan Clark[5] and Marie Ranson[1]

[1] Illawarra Health & Medical Research Institute
[2] The Kinghorn Centre for Clinical Genomics
[3] Royal Prince Alfred Hospital
[4] National Cancer Centre Singapore
[5] Chris O'Brien Lifehouse

Background: Cutaneous squamous cell carcinoma (cSCC) is an extremely common and morbid skin cancer with metastatic spread indicated in up to 5% of cases. Despite its significant burden, little is known regarding its sporadic pathogenesis or optimal treatment strategies. Patient-derived cell cultures (PDCCs) are a valuable tool which enables us to investigate disease biology; alas next to no cell lines of metastatic cSCC exist. Critics argue that cell lines are poor models due to the significant changes incurred through 2D culture. Because of this, extensive validation must be performed.

Aims: To establish novel PDCCs of metastatic cSCC and assess their validity as preclinical models of disease on the basis of genetic and phenotypic drift.

Methods: PDCCs were crafted from excised nodal cSCC metastases. Nude mice were inoculated with cells to determine their tumorigenic ability. Genetic information was acquired through interrogation with a 770 gene cancer progression panel from NanoString and whole-genome sequencing (WGS).

Results: Many pathways involved in cancer progression were found to be downregulated *in vitro* compared to their clinical counterpart. However, gene expression was mostly restored in the xenograft model. Genes harbouring high impact mutations, determined from WGS, were found to be mostly conserved across all samples, suggesting influential mechanisms for carcinogenesis were unaffected. Additional variants were detected in the PDCCs, but likely due to increased purity than genetic drift. Mutational signature frequency was found to closely match between samples.

Conclusions: We have successfully generated novel PDCCs of metastatic cSCC. Multi-omic comparisons to clinical samples revealed that whilst certain pathways are down regulated *in vitro*, expression can be restored in an animal model with conserved function of influential genes. This validation allows us to use these models as platforms for preclinical high-throughput drug and biomarker discovery with a greater degree of certainty in translation to *in vivo* systems.

The effect of exercise intensity on inflammation in cancer survivors

Briana Clifford[1], David Simar[1], Benjamin Barry[2], Justin Lees[1], Gila Moalem-Taylor[1] and David Goldstein[3]

[1] University of New South Wales
[2] University of Queensland
[3] UNSW Sydney

BACKGROUND: Systemic inflammation in cancer survivors is associated with poorer treatment outcomes and reduced survival. Exercise has been reported to have anti-inflammatory properties, although the appropriate intensity required to maximise the anti-inflammatory effects of exercise is yet to be identified.

AIM: Investigate the effect of exercise on systemic inflammation in cancer survivors.

METHOD: We recruited 10 cancer survivors (56.5 ± 9.8 years old) who had been diagnosed with breast, colorectal, prostate cancer or lymphoma and were 3-12 months post completion of adjuvant treatment. Participants completed 6 exercise sessions over two weeks at either LOW intensity (30-40% Heart rate reserve [HRR]) or HIGH intensity (60-70% HRR, 15-20 mins), underwent a 6-week washout period of no exercise and returned to complete the opposing intervention. Blood samples were collected immediately prior to the initial exercise session and 24 hours after the 6th exercise session for both exercise intensities to assess cytokines and chemokines levels in serum.

RESULTS: Low or high intensity exercise significantly altered the levels of several chemokines, without affecting key pro- or anti-inflammatory cytokines. High intensity exercise increased chemokines CCL22 (mean ± SD: 0.096 ± 0.123 pg/ml; Cohens-d (95% CI): 0.897 (0.057 - 1.700), $p<.05$) and CXCL12 (0.078 ± 0.113 pg/ml; 0.926(-0.021 - 1.834), $p= 0.56$), whereas low intensity exercise decreased MCP4 (-0.181 ± 0.211 pg/ml; -1.3(-2.387 - -0.163), $p<0.05$), CCL24 (-0.131 ± 0.160 pg/ml; -1.1(-2.135 - -0.106), $p<0.05$), and CCL27 (-0.229 ± 0.305 pg/ml; -1.14 (-2.192 -0.043) , $p<0.05$), levels.

CONCLUSION: The results of our pilot study suggest that exercise can have a modulatory effect on chemokines associated with tumour progression and recurrence, however, functional assays are needed to confirm these findings. This study contributes to the understanding of how exercise intensity may modulate circulating cytokine/chemokine profile and may impact on the clinical application of exercise in cancer survivors.

Hepatic metastases from breast cancer: liver extracellular matrix controls growth, invasion and drug sensitivity

Anna Guller[1,2,3,4], Vlada Rozova[1,2,5], Annemarie Nadort[1,2], Zahra Khabir[1,2], Inga Kuschnerus[1,2], Alfonso Garcia-Bennett[1,2], Liuen (Olivia) Liang[1,2], Yi Qian[1], Ewa Goldys[6] and Andrei Zvyagin[1,2,4]

[1] Macquarie University
[2] ARC Centre of Excellence for Nanoscale BioPhotonics
[3] University of New South Wales
[4] Sechenov University
[5] Nizhny Novgorod State University
[6] UNSW Australia

Background. Triple negative breast cancer (TNBC) has high rates of hepatic metastases unexplainable by the circulation patterns. Hypothetically, some local liver-specific factors may contribute to the observed phenomena. However, the analysis of these mechanisms is experimentally challenging because of lack of reliable methodologies, allowing to observe colonization and tumor behaviour within the organ microenvironment.

Aim. This study explores the growth dynamics, metastatic colonization and the drug responses of TNBC cells growing in three-dimensional (3D) liver-specific extracellular matrix (LS-ECM) by repurposing of tissue engineering methodology as the disease modelling approach.

Methods. Acellular liver scaffolds preserving the LS-ECM composition and architecture were created by original whole-organ decellularization procedure. Next, the scaffolds were seeded with human TNBC cells (MDA-MB-231) and cultured for 28 days as 3D tissue engineering constructs (TECs) to reproduce early stages of metastatic colonization of the liver *in vitro*. Growth dynamics and treatment efficiency of doxorubicin (Dox) and Dox-loaded mesoporous silica nanoparticles were evaluated in comparison to matching monolayer (2D) cultures. Combined histopathological examination and image analysis were employed to investigate the invasion of cancer cells in LS-ESM. *In vivo* angiogenic assay was used to validate the model.

Results. The TECs demonstrated histologically relevant structure of metastatic TNBC *in vitro* and high angiogenic potential *in vivo*. The growth rate and the drug sensitivity of TNBC cells were significantly decreased in TECs in comparison to 2D cultures. TNBC cells revealed alternative attachment and migration behavior in stromal and parenchymal compartments of the LS-ECM during the first 3 weeks, followed by reorganization and total colonization of the matrix.

Conclusions. A new biologically accurate model of hepatic TNBC metastases was validated *in vitro* and *in vivo* and demonstrated LS-ECM control of tumor growth, invasion and drug sensitivity. These observations may have important implications for diagnosis and treatment of TNBC metastases to the liver.

A novel cancer stem cell-targeted therapy characterised in highly translatable xenograft models of acute leukaemia

Basit Salik[1], Patrick Connerty[1] and Jenny Wang[1]

[1] Cancer and Stem Cell Biology Group, Children's Cancer Institute, Lowy Cancer Research Centre, University of New South Wales, Sydney, NSW 2052, Australia

Background: Acute myeloid leukaemia (AML) is an aggressive disease resulting in the highest number of leukaemia-associated deaths. Despite high response rates to induction chemotherapy, the vast majority of patients relapse after complete remission. Tumour relapse is believed to be caused by rare tumour-initiating cells with stem cell properties (called cancer stem cells) that evade conventional chemotherapy. In AML, novel strategies to target leukemic stem cells (LSCs) will have major clinical implications.

Aim: Elucidating the essential pathway components hold the key to selective targeting of LSCs in AML. Increasing evidence suggests that the Wnt/β-catenin signalling pathway is important for LSC development in AML but is not critical for the self-renewal of normal adult haematopoietic stem cells (HSCs), representing a valuable therapeutic target. However, due to its localisation and structure, β-catenin remains difficult to target. This study aims to identify novel targetable cell surface effectors regulating β-catenin signalling as 'druggable' therapeutic targets for treatment of AML with poor prognosis.

Results and Conclusion: We have identified a novel β-catenin regulator, Lgr4, a member of the G protein-coupled receptor family that represents a highly tractable class of drug targets. Genome-wide gene expression analysis of AML patient samples revealed a 3-fold increase in expression of Lgr4 in leukemic cells compared to normal haematopoietic stem cells. Here we showed that Lgr4/β-catenin signalling is a key determinant in sustaining high LSC self-renewal in vivo and its constitutive activation was pro-leukaemogenic. Our data demonstrated that genetic depletion of Lgr4 impaired LSC self-renewal and as a consequence, significantly delayed leukaemia onset in our highly translatable xenograft models of primary AML patients. In addition, pharmacological inhibition of this signalling pathway significantly reduced tumour burden in patient-derived xenograft models of AML. Altogether, these findings provide a very exciting proof-of-concept to support the potential use of the novel cancer stem cell-targeted therapeutic approach in future clinical applications and highlight its relevance in benefitting patients with genetically high-risk and unfavourable prognoses.

Exploring the relationship between Anxiety & Depression and Health Resource Use in Cancer Survivors.

Jackie Yim[1], Joanne Shaw[2], Rosalie Viney[1], Nicole Ezendam[3] and Alison Pearce[1]

[1] Centre for Health Economics Research and Evaluation, University of Technology Sydney
[2] Psycho-Oncology Co-operative Research Group, University of Sydney
[3] PROFILES, Tilburg University and Netherlands Comprehensive Cancer Organisation

Background: Anxiety and depression rates are higher in cancer survivors than the general community. Comorbid anxiety and depression in other clinical conditions is associated with greater healthcare resource use and costs. However, little is known about whether the same is true in the cancer population.

Aim: To determine whether anxiety or depression increase self-reported cancer-specific and/or all health resource use among cancer survivors.

Methods: Data from four Dutch population-based surveys on survivors of colorectal, endometrial, multiple myeloma and thyroid carcinoma from the PROFILES registry (n= 2,538) were assessed to determine the relationship between anxiety and depression (measured with Hospital Anxiety and Depression Scale: Normal 0-7, Mild ≥8, Moderate ≥ 11 & Severe ≥15) and health service use (measured by the number of GP and specialist contacts).Cancer survivors between 0.7-10.9 years since diagnosis and mean age of 61.1 were included in the analysis. Multiple linear regression was used to determine the association between anxiety or depression on health resource use, controlling for patient demographics, tumour type, treatments received, comorbidities and health professional visits.

Results: Higher anxiety or depression was associated with increased health resource use. When GP visits associated with cancer diagnosis were considered, moderate and severe anxiety were significant (both $p < 0.01$). For specialist visits associated with the cancer diagnosis, moderate anxiety, and mild or severe depression were significant (all $p < 0.05$). When all healthcare resource use was considered, the relationship to anxiety and depression was stronger. More comorbidities, lower education, tumour type and more recent diagnosis were also statistically significantly associated with increased GP or specialist visits.

Conclusions: Cancer survivors with anxiety or depression are associated with increased health service use. Greater efforts in managing anxiety and depression in cancer survivors will not only improve their quality of life but may also reduce potentially avoidable costs to the health system.

Impact of physical appearance changes among adolescents and young adults after a cancer experience

Mary-Ellen Brierley[1,2], Ursula Sansom-Daly[1,2], Julia Baenziger[1,2,3] and Claire Wakefield[1,2]

[1] Behavioural Sciences Unit, Kids Cancer Centre, Sydney Children's Hospital, NSW, Aust
[2] School of Women's and Children's Health, UNSW Sydney, NSW, Australia
[3] Department of Health Sciences & Health Policy, University of Lucerne, Switzerland

Background: Transition to cancer survivorship signals a series of challenges. In adolescents and young adults (AYAs), poor body image may be one driver of additional distress. Current scientific literature lacks a depth of understanding concerning the ongoing impact of physical appearance changes on AYA survivors.

Aim: We explored physical appearance changes resulting from AYA survivors' cancer experiences, including the frequency and nature of changes, with the aim of understanding the impact of physical appearance changes on AYAs' body image, distress and behaviours.

Methods: We recruited AYAs (15-25 years old at diagnosis) who had completed curative cancer treatment in the preceding 1-24 months from ten hospitals and cancer services across Australia. Using semi-structured interviews, we asked participants about physical appearance changes resulting from their cancer experience. We used content and iterative thematic analyses to explain experiences.

Results: Forty-three AYA survivors (51% male, mean age=21 years, mean time since diagnosis=2 years) completed an interview. Three main themes emerged; participants discussed physical appearance changes following cancer, how they felt about their appearance, and the psychosocial impact of changed appearance. Eighty-eight percent (n=38/42) of participants reported that their physical appearance had changed as a result of their cancer and/or their treatment (most commonly: alopecia (36%, n=15/42), scarring (33%, n=14/42) and weight gain (26%, n=11/42)). Twenty-four percent (n=10/42) of participants acknowledged, unsolicited, that they were dissatisfied with their body. Other psychosocial impacts included feeling a loss of identity, not being recognised by others after their cancer treatment, and feeling helpless to change appearance.

Conclusion: Our results have translational significance for the care of AYA survivors. Body image concerns should be considered as a potential barrier to successful reintegration post cancer treatment. AYAs may benefit from familial and peer support, healthy lifestyle interventions, and clinical environments being sensitive to appearance-related concerns.

Detection of AR-V7 in ctRNA of castrate resistant prostate cancer patients.

Mohammed Nimir[1,2], Yafeng Ma[3,4], Sarah Jeffreys[3,5,4], Thomas Opperman[1,2], Francis Young[3,4], Pei Ding[3,4], Wei Chua[1], Bavanthi Balakrishnar[1], Adam Cooper[1], Therese Becker[3,4] and Paul De Souza[6,7,8]

[1] Ingham Institute
[2] UNSW
[3] Ingham Institute for Applied Medical Research
[4] Centre for Circulating Tumour Cell Diagnostics and Research
[5] Western Sydney University
[6] WSU
[7] IIAMR
[8] Liverpool Hospital

Background: Resistance to first line androgen deprivation therapy (ADT) is a major challenge in prostate cancer (Pc) treatment. Changes to the androgen receptor, such as expression of the variant 7(AR-V7), are emerging mechanisms of therapy resistance. While our team has established highly sensitive AR-V7 detection from circulating tumor cells (CTCs), its detection from circulating tumor RNA (ctRNA), would be more convenient and economic.

Aims: To establish a method to detect AR-V7 and full-length androgen receptor (FL-AR) in Pc patient ctRNA.

Methods:

1. Seven RNA purification kits were compared for ctRNA isolation.
2. The best performing kit is currently used to test for FL-AR, AR-V7 in a cohort of Pc patients.

Results:

- Testing of ctRNA extraction kits has revealed that the Qiagen Nucleic Acid kit is superior in the detection of FL-AR, AR-V7 and GAPDH.
- Four Pc patients known to express AR-V7 have been recruited and five parallel blood samples of each are currently compared to determine how long blood can be stored prior to AR-V7 detection from ctRNA.
- Detection of AR-V7 and FL-AR from ctRNA of stored plasma samples is currently under way and ctRNA-based FL-AR and AR-V7 status will be correlated to patient outcome.

Conclusion: This study has shown that the detection of AR-V7 from plasma ctRNA is feasible. We predict that AR-V7 detection from ctRNA will correlate with disease outcomes and may provide a non-invasive, economic test for this emerging Pc biomarker. Such a test can be undertaken to stratify patients for clinical trials of novel drugs targeting AR-V7 positive CRPC.

Breast cancer screening using tomosynthesis or mammography: A meta-analysis of cancer detection and recall

Luke Marinovich[1], Kylie Hunter[2,3], Petra Macaskill[3] and Nehmat Houssami[3]

[1] Sydney School of Public Health, University of Sydney
[2] NHMRC Clinical Trials Centre
[3] Sydney School of Public Health

Background: Tomosynthesis approximates a 3D-mammogram of the breast, reducing parenchymal overlap that masks cancers or creates false "lesions" on 2D-mammography, and potentially enabling more accurate detection of breast cancer.

Aim: To compare breast cancer screening detection and recall in asymptomatic women for tomosynthesis versus 2D-mammography.

Methods: A systematic review and random-effects meta-analysis was undertaken. Electronic databases (2009 - July 2017) were searched for studies comparing tomosynthesis and 2D-mammography in asymptomatic women attending population breast cancer screening, and reporting cancer detection rate (CDR) and recall rate. All statistical tests were two-sided.

Results: 17 studies (1,009,790 participants) were included from 413 citations. The pooled incremental CDR for tomosynthesis was 1.6 cancers per 1,000 screens (95%CI 1.1, 2.0; $P<0.001$; $I^2=36.9\%$). Incremental CDR was statistically significantly higher for European/Scandinavian studies, all using "paired" design where women had both tests (2.4 per 1,000 screens; 95%CI 1.9, 2.9; $P<0.001$; $I^2=0.0\%$) compared with US ("unpaired") studies (1.1 per 1,000 screens; 95%CI 0.8, 1.5; $P<0.001$; $I^2=0.0\%$) ($P<0.001$ between strata). Recall rate for tomosynthesis was statistically significantly lower than for 2D-mammography (pooled absolute reduction -2.2%; 95%CI -3.0, -1.4; $P<0.001$; $I^2=98.2\%$). Stratified analyses showed a decrease in US studies (pooled difference in recall rate -2.9%; 95%CI -3.5, -2.4; $P<0.001$; $I^2=92.9\%$) but not European/Scandinavian studies (0.5% increase in recall, 95%CI -0.1, 1.2; $P=0.12$; $I^2=93.5\%$) ($P<0.001$ between strata). Results were similar in sensitivity analyses excluding studies with overlapping cohorts.

Conclusions: Tomosynthesis improves CDR and reduces recall; however, effects are dependent on screening setting, with greater improvement in CDR in European/Scandinavian studies (biennial screening), and reduction in recall in US studies with high baseline recall.

Optimising Dose via TDM: Mitotane as a Model for Implementation of Personalised Therapy

Madhu Garg[1,2,3], Jennette Sakoff[1,2,4], Ji Woong Yoo[4,2,3], Jennifer Martin[4,3,2] and Stephen Ackland[1,4,2]

[1] Dept. of Medical Oncology, Calvary Mater Newcastle Hospital, NSW 2298 Australia
[2] Hunter Cancer Research Alliance (HCRA), Newcastle, NSW, Australia
[3] Hunter Medical Research Institute (HMRI), Newcastle, NSW, Australia
[4] University of Newcastle, Callaghan, NSW 2308 Australia

Background: In oncology, Therapeutic Drug Monitoring (TDM) is not standard practice for most cytotoxic agents. Evidence for benefit for TDM of mitotane in adrenocortical cancer (ACC) was developed in Europe, and included in the 2012 ESMO management guidelines for neuroendocrine tumours. We developed an assay for measuring plasma mitotane concentrations and promoted it to Australian medical oncologists and endocrinologists as a gratis service for their patients with ACC.

Methods & Results: Over several years, we have assayed ~150 mitotane samples pa and provided recommendations for dose changes in order to achieve a fast and stable therapeutic plasma concentration (Cp) of 14-20 mg/L. In our clinical study so far (n=37, M/F 19/18 including 4 children), a therapeutic Cp was achieved in 5.4±3.8 months (n=18) in adults and 2.3±1.3 months in children (n=3). The dose required to achieve therapeutic Cp is 5.6±3.5 g/d for adults (3.8±0.8g/d for children). We have defined a TDM schedule to rapidly achieve Cp of 14-20 and to dose-reduce and monitor if >20 mg/L. BMI affects the relationship between ideal dose and Cp.

Conclusions: Mitotane TDM could now be promoted as a biochemistry MBS item. Ongoing research will allow refinement of the dosing recommendation algorithm to improve dosing precision and speed. Mitotane can serve as a model for development of TDM services in Australia for a range of old and new medicines particularly anticancer drugs. In the past, TDM of most anticancer drugs was slow, resource-intensive and not widely used. Modern technologies make this approach feasible and cost-effective, leading to better drug use and less toxicity.

Translational significance: We are now poised to promote this TDM facility to all oncology/endocrinology services in Australia. Beneficiaries are patients with ACC, their physicians and the community at large, by better control of this cancer, and reduced toxicity and cost of care.

Geographic variations in time to diagnosis and treatment of head and neck cancer in NSW

Rebecca Venchiarutti[1,2], Carsten E Palme[3,4,5], Jonathan R Clark[3,4,5] and Jane M Young[1,2,4]

[1] The University of Sydney, Faculty of Medicine and Health, Sydney School of Public Health, NSW, Australia
[2] Surgical Outcomes Research Centre (SOuRCe), Royal Prince Alfred Hospital, NSW, Australia
[3] Sydney Head and Neck Cancer Institute, Chris O'Brien Lifehouse, NSW, Australia
[4] RPA Institute of Academic Surgery, Sydney Local Health District, NSW, Australia
[5] The University of Sydney, Faculty of Medicine and Health, NSW, Australia

Background: More than 50% of head and neck cancers (HNCs) are diagnosed at advanced stage. Regional/remote HNC patients have poorer survival than their metropolitan counterparts, and are less likely to utilise radiotherapy for treatment. Patient and health-system factors may hinder early cancer diagnosis, reflected in longer time intervals along the pathway to treatment.

Aim: To examine geographical variations in pathways to diagnosis and treatment for patients with HNC in NSW, and implications for survival.

Methods: Patients diagnosed with squamous cell carcinoma (SCC) of the oral cavity, oropharynx, or cutaneous SCC from 1st July 2008 to 30th June 2013 were identified from a major metropolitan referral hospital. Study data were retrospectively collected by audits of medical records and a dedicated HNC database.

Results: Two hundred and forty-eight patients were eligible (78% male), mean (SD) age was 63.9 (13.1) years, and 68% were diagnosed as advanced stage. At diagnosis, 75%, 24% and 1% lived in metropolitan, regional and remote NSW, respectively. Fourteen per cent of patients lived >100km from a hospital with a HNC multidisciplinary team (median [IQR] distance 5.6km [5.8km] for metropolitan patients and 107.5km [138.4km] for regional/remote patients). Total interval (from symptom onset to treatment) was longer among regional/remote patients compared to metropolitan patients (median 5.6 and 3.5 months respectively, P=0.013). Time from symptom onset to diagnosis was longer among regional/remote patients vs metropolitan patients (median 4.3 and 2.3 months respectively, P=0.027). Median treatment interval (diagnosis to treatment) and overall survival did not differ by remoteness.

Conclusions: Regional/remote HNC patients experience longer time to diagnosis and treatment than metropolitan patients. We are currently investigating patient and health-system factors that facilitate and impede early HNC diagnosis, and findings will be used to develop potential interventions and inform health policy to improve timely HNC diagnosis and treatment in regional/remote NSW.

Studies on antitumour activity of novel platinum alone and in combination with selected tumour active phytochemical

Yahya Solayman[1], Fazlul Huq[2], Philip Beale[3], Laila Arzuman[2] and Jun Qing Yu[2]

[1] The University of Sydney
[2] Discipline of Biomedical Science, School of Medical Sciences, Sydney Medical School, University of Sydney
[3] Department of Medicine, Sydney Medical School, University of Sydney

Background: Platinum-based chemotherapeutics such as cisplatin and oxaliplatin are routinely used in the clinic to treat various types of cancers including ovarian and colorectal cancers. However, presence of side-effects, intrinsic and/or acquired drug-resistance can compromise their therapeutic effectiveness. With the aim of improving the safety profile and broadening the spectrum of activity, many rule breaker platinums were prepared by changing the nature of the leaving groups and carrier ligands. This also includes mono-functional platinum (LH5) that has only one leaving group. One such compound has shown greater activity than cisplatin against platinum refractory ovarian cancer cell lines. Recently, there has been growing interest in the use of phytochemicals present in fruits, herbs and spices and other plant sources in the prevention and treatment of cancer. These tumour active compounds exert their therapeutic actions through cell signalling pathways different from those of platinum derivatives making them logical candidates for combination with platinum drugs towards synergistic outcomes in cell kill. It is thus thought the combinations can provide an affordable means of overcoming drug resistance and reducing the side effects.

Aim: The present study aims to apply combinations of LH5 with selected phytochemicals including Camptothecin to ovarian and colorectal cancer cell lines and explore the outcomes of combined drug action.

Methods: The study utilises cell culture, MTT reduction assay, sequenced binary combinations, combination index analysis and drug-DNA binding, cellular accumulation, gel electrophoresis, and proteomics.

Results: Antitumour activities of LH5 analogue against ovarian and colorectal cancer cell lines and results from binary combination with selected phytochemicals and other platinum drugs will be presented in a poster. The results thus far show that LH5 in combination with Camptothecin produces sequence dependent synergism in ovarian tumour models.

Conclusions: Synergism from combination of LH5 with Camptothecin indicates this can overcome drug resistance.

Targeting ABCE1 disables MYC-driven protein synthesis to block neuroblastoma progression

Jixuan Gao[1], Katherine Hannan[2], Jamie Fletcher[3], MoonSun Jung[3], Eric Kusnadi[4], Richard Pearson[4], Ross Hannan[2], Michelle Haber[3], Murray Norris[3], Klaartje Somers[3] and Michelle Henderson[3]

[1] Children's Cancer Institute
[2] Australian National University
[3] Children's Cancer Institute
[4] Peter MacCallum Cancer Centre

Background: Neuroblastoma is the most common extracranial solid tumour in children. High-risk neuroblastomas with *MYCN* gene amplification have a devastating five-year survival of ~11%. MYCN and c-MYC are related transcription factors that heighten protein synthesis to drive cancer progression. Despite the heavy reliance of MYC-driven cancers on elevated protein synthesis, inhibiting mRNA translation to treat *MYCN*-amplified neuroblastoma has never been explored. The ABCE1 translation factor is directly up-regulated by MYCN and powers ribosome recycling to promote translation re-initiation and the perpetual protein synthesis required for cancer growth and metastasis. Furthermore, high tumour *ABCE1* expression is correlated with reduced survival of neuroblastoma patients. ABCE1 is thus a putative therapeutic target.

Aim: To investigate whether targeting ABCE1-mediated translation can block neuroblastoma progression.

Method: ABCE1 was suppressed using siRNAs. Polysome profiling and puromycin incorporation assays measured protein synthesis. BrdU incorporation, colony-forming and Transwell assays measured cell proliferation, growth and migration respectively. Mice xenografted with neuroblastoma-derived cells expressing ABCE1-specific shRNA measured tumour growth.

Results: Forced *MYCN* expression in SH-EP Tet21N neuroblastoma cells dramatically enhanced protein synthesis but knockdown of ABCE1 abolished this increase, returning protein synthesis to levels observed in cells without *MYCN* expression. Striking reductions in translation efficiency were observed in multiple *MYCN*-amplified neuroblastoma lines following ABCE1 suppression ($P<0.0001$), along with severely impaired cell proliferation, long-term growth and migration ($P<0.001$). Protein synthesis and the growth of neuroblastoma cells without *MYCN* amplification and non-malignant cells are not affected by ABCE1 knockdown, indicating the presence of a possible therapeutic window. Notably, in mice xenografted with *MYCN*-amplified neuroblastoma cells, ABCE1 suppression delayed tumour growth at both subcutaneous and metastatic sites ($P<0.001$), prolonging the survival of tumour-bearing mice.

Conclusion: Targeting ABCE1-mediated translation selectively blocks the progression of *MYCN*-amplified neuroblastoma and highlights ABCE1 as a valuable therapeutic target in this disease.

Fifty shades of radiobiology: alpha/beta ratios exposed

Ana Esteves[1], Linda Rogers[1], David McKenzie[2] and Natalka Suchowerska[1]

[1] Chris O'Brien Lifehouse
[2] The University of Sydney

Background: In classical radiobiology, the linear-quadratic (LQ) model has been traditionally used as a mechanistic model to explain cell killing and predict the survival of cells exposed to radiation. The alpha and beta parameters that can be derived from the LQ formalism are universally used in clinical practice to inform the selection of the fractionation schedules to be delivered to cancer patients during their radiotherapy treatment.

Aim: A fairly wide range of in vivo endpoints are used for LQ predictions. In vitro systems are the most straightforward to obtain but the study conditions are obviously far from realistic. It is uncertain how well in vitro estimations overlap in vivo parameters and how much information can be extended to in vivo systems and clinical applications. In this study, we examined the reliability of the calculated values of these parameters for common cancers such as breast, prostate and lung.

Methods: We determined the clonogenic survival of a range of cell lines exposed to several radiation doses and estimated their respective alpha and beta parameters by fitting the dose response data to the linear quadratic model.

Results: Our results identify the need for alpha/beta ratios to be reported to the specific conditions that they have been determined. We show that alpha/beta estimations are largely affected by assay-dependent conditions, such as the radiation dose regime chosen, seeding density and endpoint, estimation method and intrinsic biological variabilities, with cell lines of the same cancer subtype having different alpha/beta ratios.

Conclusions: These results highlight that the applicability of the linear quadratic model in clinical radiotherapy is limited by the difficulty in obtaining accurate parameter estimations. Do they truly reflect the efficacy of a particular radiation treatment schedule and what are the alternatives?

Mathematical modelling of cancer cell morphological and phenotypic plasticity in response to the extracellular matrix

Vlada Rozova[1,2], Anna Guller[1,3,2], Ayad Anwer[1,3,4] and Andrei Zvyagin[1,2]

[1] Macquarie University
[2] ARC Centre of Excellence for Nanoscale BioPhotonics
[3] University of New South Wales
[4] ARC Centre of Excellence for Nanoscale Biophotonics

Tissue engineering constructs (TECs) composed from organ-specific extracellular matrix (ECM) and the normal or malignant cells of choice provide a powerful in vitro platform allowing more realistic and sustainable modelling of various aspects of normal morphogenesis, cancer progression, and the drug effects in reconstructed tissues. However, currently available approaches for evaluation of the tissues' structure rely on laborious pathological examination and cannot be easily translated to the high-throughput research and industrial applications. Therefore, there is a strong demand to develop computer-aided methods allowing extraction and analysis of the meaningful biological information from the routinely processed histological samples.

As an initial step to solve this problem, we performed digital analysis of histological images of TECs, representing original three-dimensional tissue engineering models of triple negative breast cancer metastases to the liver, created in our group and cultured in vitro for 4 weeks. TECs provide reduced tissue complexity allowing deciphering of the key features of cellular dynamics in realistic tissue environment. As a result, we developed a mathematical model of the effects of host organ ECM on initial cellular attachment, cellular morphology and subsequent matrix colonisation patterns. Further, to expand the computational model and attribute the role of the underlying ECM to cell invasion and clustering inside the tissue, we ran a set of single-factor experiments, each designed to reveal the effect of a specific physical property of the matrix. Statistical analysis of the experimental data provides estimations of model parameters and complements the picture of cell-matrix interactions.

We believe that this data-driven approach will allow predicting phenotypical and morphological changes of cancer cells and the subsequent preferred mode of tissue colonisation, which is essential for the choice of appropriate treatment.

Inhibition of the tumour suppressor PP2A-B55α induces aggressive and therapy resistant phenotype in breast cancer

Abdul Mannan[1,2], Severine Roselli[1,2], Richard G. S. Kahl[1,2], Simon King[2], Megan Clarke[2], Kathryn Skelding[1,2], Matthew D. Dun[1,2] and Nicole M. Verrills[1,2]

[1] School of Biomedical Sciences and Pharmacy, and the Priority Research Centre for Cancer Research, Translation and Innovation, University of Newcastle, Callaghan, NSW, Australia
[2] Cancer Research Program, Hunter Medical Research Institute, New Lambton, Newcastle, NSW, Australia

Background: Over 3,000 Australian women die from breast cancer every year, thus improved therapies are needed. Recent genomic analyses of breast tumours have revealed recurrent deletion of the *PPP2R2A* gene, which encodes the PP2A-B55α regulatory subunit of the serine/threonine protein phosphatase, PP2A. *PPP2R2A* deletion was most common in luminal B (ER^+) tumours, a subtype of breast tumour, which respond poorly to current therapies. Our recent data has further shown that PP2A-B55α protein expression is low in aggressive breast tumours.

Aim: To reveal the impact of PP2A-B55α loss on breast cancer aggression and sensitivity to targeted therapies.

Methods: The expression of PP2A-B55α was reduced using shRNA-mediated knockdown in tamoxifen-sensitive MCF7 and -resistant BT474 human breast cancer cell lines. The effects of knockdown on cell proliferation, anchorage independent growth, migration, invasion, activation of signalling pathways, and sensitivity to tamoxifen, lapatininb and/or PP2A activating drugs, were assessed.

Results: PP2A-B55α knockdown induced increased proliferation, anchorage independent growth and resistance to tamoxifen in MCF7 cells. Mechanistically, this was associated with increased pERα (S167), HER3 and FAK protein expression. In addition, knockdown of PP2A-B55α in the $HER2^+$ cell line, BT474, enhanced transwell migration and invasion, accompanied by increased expression of epithelial to mesenchymal transition (EMT) marker proteins, and induced lapatinib resistance. Importantly however, PP2A-B55α-knockdown cells were sensitive to PP2A activating drugs. Furthermore, the addition of PP2A activating drugs sensitized the resistant cells to tamoxifen and lapatanib, suggesting a possible therapeutic option for patients with PP2A-B55α-low tumours and/or drug-resistant tumours.

Conclusion: This study suggests that the loss of tumour suppressive PP2A-B55α induces aggressive and therapy resistant breast cancer that may be targetable by PP2A activators.

Targeting DNA-PK sensitises FLT3-mutant acute myeloid leukaemia to tyrosine kinase inhibitors

Heather Murray[1], Anoop Enjeti[2], Richard Kahl[3,4], Hayley Flanagan[1], Juhura Al Mazi[1], Nathan Smith[5], Charles De Bock[6], Martin Larsen[7], Nicole Verrills[3,4] and Matthew Dun[8]

[1] Cancer Research Program, Hunter Medical Research Institute, and School of Biomedical Sciences and Pharmacy Faculty of Health and Medicine, University of Newcastle, Callaghan, NSW, 2308, Australia
[2] Calvary Mater Hospital, Newcastle, 2298, NSW, Australia
[3] School of Biomedical Sciences & Pharmacy, University of Newcastle, Callaghan, NSW, Australia
[4] Hunter Medical Research Institute Cancer Research Program, New Lambton, Newcastle, NSW, Australia
[5] Analytical and Biomolecular Research Facility Advanced Mass Spectrometry Unit, University of Newcastle, Callaghan, NSW, 2308, Australia
[6] VIB Center for the Biology of Disease, and KU Leuven Center for Human Genetics, Leuven 3000, Belgium
[7] Department of Molecular Biology and Biochemistry, Protein Research Group, University of Southern Denmark, Odense, 5230, Denmark
[8] Cancer Research Program, Hunter Medical Research Institute, and School of Biomedical Sciences and Pharmacy Faculty of Health and Medicine, University of Newcastle, Callaghan, NSW, 2308, Australia. *These authors have contributed equally to this work

Background: Acute myeloid leukaemia (AML) is the most common and aggressive form of acute leukaemia, with a 5-year survival rate of just 24%. Activating mutations in the receptor tyrosine kinase, FLT3, are the most common recurring mutations in AML (25-30% of patients). Inhibiting the FLT3 receptor as a mono-therapeutic strategy in AML has proven difficult however, with the development of treatment resistance and relapse. In order to identify improved therapeutic targets, the oncogenic signalling pathways downstream of mutant FLT3 require characterisation.

Aim: Identify druggable, oncogenic signalling pathways downstream of mutant FLT3 using unbiased phosphoproteomic profiling

Methods: Quantitative phosphoproteomics was performed on primary blasts from 7 AML patients (4 FLT3-mutant, 3 FLT3-wildtype), and differentially phosphorylated pathways were identified using Ingenuity Pathway Analysis. Validation of results was performed in a panel of cell lines using targeted mass spectrometry. Proliferation, annexin, and cell cycle assays were used to assess drug toxicity; drug synergy was evaluated using Chou-Talalay and Webb analyses.

Results: Analysis of differentially expressed phosphoproteins in FLT3-mutant compared to FLT3-wildtype AML patient blasts revealed dysregulation of DNA repair pathways. Specifically, FLT3-mutant samples displayed increased phosphorylation of proteins within the error-prone Non-Homologous End Joining (NHEJ) repair pathway, indicating NHEJ pathway activation. Accordingly, proliferation assays revealed that FLT3-mutant cell lines were sensitive to inhibition of the NHEJ core kinase, DNA-PK. Inhibition of DNA-PK kinase activity combined with inhibition of the FLT3 receptor led to synergistic induction of cell death, selectively in FLT3-mutant cell lines. DNA-PK inhibitors combined with FLT3 inhibitors also co-operatively induced cell death in FLT3-mutant primary AML patient samples *ex vivo*.

Conclusions/Significance: FLT3-mutant AML is associated with activation of the error-prone NHEJ repair pathway, which may contribute to genomic instability. Targeting the NHEJ kinase, DNA-PK, in combination with FLT3 inhibitors has the potential to improve patient outcomes for this poor-prognosis AML subtype.

Protein Phosphatase 2A as a druggable target for breast cancer treatment.

Nikita Panicker[1,2], Severine Roselli[1,2], Richard Kahl[1,2], Lauren Watt[1,2], Abdul Mannan[1,2] and Nicole Verrills[1,2]

[1] School of Biomedical Sciences & Pharmacy, University of Newcastle, Callaghan, NSW, Australia
[2] Hunter Medical Research Institute Cancer Research Program, New Lambton, Newcastle, NSW, Australia

Background: Breast cancer is characterised by the de-regulation of multiple cellular signalling pathways (e.g.RAS/MAPK, PI3K/Akt, homologous recombination repair) which in normal cells are tightly regulated by protein kinases and phosphatases. The tumour suppressor serine/threonine phosphatase PP2A is a negative regulator of these pathways. The *PPP2R2A* gene, encoding the PP2A regulatory subunit PP2A-B55α is commonly deleted in breast tumours, and low PP2A-B55α associates with aggressive, poor prognosis breast tumours. However, the functional role of PP2A-B55α loss in breast cancer is not known.

Aim: To investigate the functional role of PP2A-B55α in breast tumourigenesis.

Methods: The effect of shRNA-mediated knockdown of PP2A-B55α in normal mammary epithelial MCF10A cells and MCF7 breast cancer cells was examined using standard and 3D-cultures. The effect of PP2A activating drugs in a panel of breast cancer cell lines was examined using cytotoxicity assays, and in an orthotopic xenograft mouse model of aggressive breast cancer (MDA-MB-231). A novel constitutive PP2A-B55α knockout mouse was generated and crossed with MMTV-Neu transgenic mice to characterise the effect of reduced PP2A-B55α on mammary gland development/tumour formation.

Results: PP2A-B55α knockdown induced a tumourigenic phenotype in MCF10A 3D-cultures, and increased proliferation and colony formation in MCF7 cells, associated with enhanced Akt and ERK signalling. Constitutive homozygous knockout of PP2A-B55α was lethal post embryonic day 18.5, with evidence of epidermal/neural tube defects. Viable, adult heterozygous mice displayed decreased mammary gland branching. Analysis of breast tumour onset/growth in MMTV-Neu mice with heterozygous PP2A-B55α expression is ongoing. Treatment with PP2A activating drugs significantly inhibited breast tumour growth and metastases in human breast cancer cell lines *in vitro* and *in vivo*.

Conclusions: We show that PP2A-B55α is essential for mammalian development and functionally important as a breast tumour suppressor. We further showed that pharmacological activation of PP2A is a potential therapeutic strategy for poor prognosis breast cancer patients.

Investigating the Genetics of the Development of Lung Cancer

Vrushali Chimankar[1,2], Celeste Harrison[1,2], Atiqur Rahman[1,2], Sophie Pickles[1,2], Priyanka Sahu[1,2], Helle Bielefeldt Ohmann[3], Neil Watkins[4] and Philip Hansbro[1,2]

[1] University of Newcastle
[2] Hunter Medical Research Institute
[3] University of Queensland
[4] Garvan Institute of Medical Research

Background: Lung cancer (LC) is the leading cause of cancer-related morbidity and mortality in Australia and worldwide. Cigarette smoking is a major risk factor for LC and accounts for 80-85% of all LC cases. It alters the expression of genes responsible for normal cellular function. LC has survival rate of only 15%. The current diagnostic techniques fail to detect LC at an early stage due to the poor understanding of genetic events leading to development of LC. Conducting genome-wide studies can identify novel mutations responsible for lung carcinogenesis that could be used as diagnostic markers.

Aims: Establishing a functional mouse model for early stage and late stage Non-Small Cell Lung Cancer (NSCLC). Identifying genetic alterations linked to the development of LC using long-term tobacco carcinogen/cigarette-smoked wild-type mouse models and validate them in short-term mouse models and human samples.
Methods: A/J mice were administered NNK (4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone) and exposed to cigarette smoke (CS) for varying periods. Whole genome sequencing (WGS) is being performed on tumour and non-tumour lung tissue from the long-term model and the results will be validated in short-term mouse models and human samples using targeted sequencing.
Results: Our group has established a novel short-term mouse model where mice exposed to NNK and 8-weeks of CS followed by 8-weeks of air rest develop adenomas resembling human bronchoalveolar adenomatous hyperplasia. In our long-term models, mice exposed to NNK and 36-weeks of CS followed by 27-weeks of air rest developed adenocarcinomas resembling human bronchoalveolar carcinomas.
Conclusions: Our novel mouse model recapitulates the crucial pathophysiological features of human LC. We anticipate that data from WGS would identify genetic alterations in pre-neoplastic stages of LC that can be developed into early diagnostics.

Translational aspect: Our interrogation of clinically relevant models will identify genomic mutations that occur during the initiation of tumour development that can be translated into early diagnostic tests for LC fitting into T1 phase of translational research pipeline.

Liquid biopsies to detect clinical breast cancer biomarkers

Sarah Jeffreys[1,2,3], Patsy Soon[1,3], Yafeng Ma[1,3], Francis Young[1,3], Pei Ding[1,3], Hans Neubauer[4], Paul De Souza[1,3] and Therese Becker[1,3]

[1] Ingham Institute for Applied Medical Research
[2] Western Sydney University
[3] Centre for Circulating Tumour Cell Diagnostics and Research
[4] Heinrich-Heine-Universität Düsseldorf

Background: Hormone receptor positive breast cancer (BC) accounts for 60-80% of all BCs, and majority of these patients are treated with Aromatase Inhibitors (AIs). However, up to 40% of these patients will relapse. Mutations in the estrogen receptor gene, ESR1 and changes in the androgen receptor (AR) are biomarkers of AI resistance.

Aims

1. To detect common ESR1 mutations, as well as other known AI resistance biomarkers, in circulating tumour cells (CTCs) from breast cancer patients treated with AIs, and to correlate presence with treatment sensitivity.
2. To develop in vitro assays for functional testing of ESR1 mutations.

Methods

1. CTCs are enriched from two EDTA blood samples from AI sensitive (n=15) and resistant (n=15) patients using the IsoFlux CTC isolation platform.
2. One CTC enriched sample is used for mRNA (AR-V7) analysis. The other immunocytostained for CTC enumeration and single CTCs isolation using the ALS CellCelector.
3. Single CTCs Whole Genome Amplifications (WGA) are tested by droplet digital PCR (ddPCR) for ESR1 mutations and AR amplification.
4. In vitro assays (estrogen dependence, promoter reporter assays and computational modelling) of ESR1 variants will confirm gain/loss of ER function are developed

Results: Patient recruitment CTC isolation and analysis has commenced. ddPCR assays for the detection of the ESR1 mutations; E380Q, Y537N/S and D538G, as well as AR biomarkers have been established. Generating In vitro assays to functionally test established and ESR1 novel mutations for their likely role in AI resistance is under way.

Conclusion: This study will be a proof of concept whether AI resistance markers are detectable from BC CTCs and will likely generate economic and clinically applicable assays for AI resistance biomarkers from liquid biopsies.

Implementation of a decision support triage tool in specialist-general practitioner shared care: an exploratory study

Kylie Vuong[1], John Lewis[1], Kate Webber[1], Jane Taggart[1], Stella Jun[1], Kerry Uebel[1] and Mark Harris[1]

[1] UNSW Sydney

Background: The conventional model for follow-up care after colorectal cancer sees patients attending for periodic review 3-6 monthly in tertiary cancer services. With growing numbers of cancer survivors, this approach is not sustainable, and data suggests that Australian survivor numbers will imminently outgrow the oncology workforce. There is evidence of equivalent outcomes for patients followed up after treatment of colorectal cancer, by general practice services when compared to specialist services.

Aims: We aimed to: (1) identify patient scenarios at 'low-intermediate risk' of complications that are suitable for shared care based on a decision support triage tool; and (2) assess perspectives from cancer specialists, general practitioners and people who have experienced colorectal cancer on the suitability of the 'low-intermediate risk' patient scenarios and resources needed to support the shared care team model.

Methods: We will use a qualitative multi-method design that combines questionnaires with semi-structured interview. Interviews will be conducted with cancer specialists, general practitioners and people who have experienced colorectal cancer.

A decision support triage tool has been developed to identify scenarios at 'low-intermediate' risk of complications and therefore suitable for shared care. The tool is based on known patient criteria that are associated with better long-term outcomes. Baseline demographics will be obtained from participating cancer specialists, general practitioners and people with colorectal cancer immediately before the interview. We will conduct in-depth semi-structured interviews on the suitability of patient scenarios for shared care and resources needed to support this model of care. Interviews will be audio-recorded, professionally transcribed and analysed thematically using a grounded theory approach.

Results: The study is in progress; preliminary results will be available at the conference.

A systematic review of unmet needs measures for people diagnosed with head and neck cancer (HNC)

Chindhu Shunmuga sundaram[1], Claudia Rutherford[1], Phyllis Butow[1], Puma Sundaresan[1] and Haryana Dhillon[1]

[1] University of Sydney

Background: HNCs have a high mortality rate, with about three million losing the battle each year. Assessing and managing diverse unmet needs of HNC patients throughout their cancer journey is critical in determining the quality of care being provided.

Aims: We aimed to examine available unmet needs measures in HNC setting and appraise them based on content and psychometric properties.

Methods: We conducted a systematic search of five electronic databases (July 2007-July 2017) to identify studies on unmet needs in HNC population. Two independent reviewers screened articles for eligibility (second reviewer screened 10% at each stage). In addition, web-based patient reported outcome (PRO) databases were searched for unmet needs measures. Those measures used in retrieved studies and identified from PRO databases were extracted, screened and reviewed for content coverage and psychometric properties. From existing measures and reviews, a conceptual framework with 12 clinically relevant aspects of unmet needs were compiled to assess the conceptual coverage of available unmet needs measures.

Results: Literature search identified 449 records of which 32 studies assessing unmet needs in HNC cancer met the selection criteria. Seven unmet needs measures were extracted from retrieved studies and eight measures from PRO databases (42 measures reviewed), a total of 15 measures were reviewed. Content mapping revealed the following three measures demonstrated excellent content validity with more than 80% conceptual coverage: Patient Concerns Inventory (PCI), Needs Assessment for Advanced Cancer Patients (NA-ACP), and James Supportive Care Screening (JSSS). Evaluation of psychometric properties revealed SUNS as the most psychometrically robust and rigorously developed measure. It is notable that most of the assessed measures demonstrated internal consistency (Cronbach alpha >0.7), except PCI and Supportive Needs Screening Tool (SNST).

Conclusions: We have identified three unmet need measures with excellent conceptual coverage but poorer psychometric properties. A fourth measure has poorer conceptual coverage but robust psychometrics. It is unclear, at this point, which is the best measure of supportive care needs to use in clinical research and practice with HNC patients.

Investigation of pyrexia in patients with BRAF V600E/K metastatic melanoma treated with dabrafenib and trametinib

Hannah Yejin Kim[1], Janna K Duong[1], Georgina V Long[2], Alexander M Menzies[2], Maria Gonzalez[3], Helen Rizos[4], Esther Lim[4], Jenny Lee[4] and Alan V Boddy[1]

[1] School of Pharmacy, University of Sydney, Sydney, NSW, Australia
[2] Melanoma Institute Australia and School of Medicine, University of Sydney, Sydney, NSW, Australia
[3] Melanoma Institute Australia, Sydney, NSW, Australia
[4] Biomedical Sciences, Faculty of Medicine and Health Sciences, Macquarie University, Sydney, NSW, Australia

Background. The combination of a BRAF inhibitor dabrafenib and a MEK inhibitor trametinib (CombiDT) has improved survival outcomes compared with chemotherapy or dabrafenib in advanced BRAF V600E/K melanoma. However, the use of CombiDT has a high incidence of pyrexia (50-70%). Understanding the etiology of pyrexia would maximise the proven benefit of CombiDT therapy.

Aim. To investigate if and to what extent the pharmacokinetics (PK) of dabrafenib and trametinib contribute to pyrexia. To investigate an association between inflammatory cytokines and pyrexia.

Methods. The study included 37 patients with Stage 3 BRAF V600E/K melanoma treated with CombiDT, recruited onto Neo Adjuvant Combi Trial (protocol ID: 200332) between August 2014 to June 2017. Blood samples were collected during the 12 weeks of neo-adjuvant treatment. Plasma concentrations of drugs and metabolites were determined using validated LCMS assays. Population PK model was applied to dabrafenib and trametinib data using NONMEM. A panel of inflammatory cytokines was also measured in patients.

Results. Dabrafenib concentrations ranged from 4.0-4628 ng/ml and trametinib from 1.0-45 ng/ml in 139 (dabrafenib) and 162 (trametinib) post-treatment samples from 34 patients. N-desmethyl-dabrafenib was the most prevalent metabolite, followed by carboxy- and then hydroxy-dabrafenib. A 2-compartment model with first-order absorption provided the best fit to the dabrafenib and trametinib data. Association between pyrexia and higher AUC or C_{min} for the drugs or higher peak metabolite ratio could not be observed from our data. Increase in Interleukin (IL)-1B and IL-6 at early days of treatment (EDT: day 4-7) from baseline were 1.9-fold ($p=0.029$) and 2.5-fold ($p=0.028$) higher respectively in pyrexia group compared to no pyrexia group.

Conclusions. In our study, potential causes of drug-induced pyrexia were investigated. However, apparent relationship between exposure to drugs or metabolites, and pyrexia was not observed. Increase in levels of IL-1B and IL-6 were observed in patients with pyrexia. A high proportion of patients with pyrexia (71%) and only 12% (4 patients) without pyrexia/treatment interruptions were limitations to observing any further apparent relationships between the investigated factors and pyrexia.

Changes in household income and employment status as a result of cancer treatment – A prospective single centre study

Anupriya Agarwal[1], Deme Karikios[2,1], Phillip Beale[3,1], Martin Stockler[3,1,4], Rachael Morton[5,6], Anthony Linton[3], Prunella Blinman[3] and Annabel Goodwin[3]

[1] University of Sydney
[2] Nepean Cancer Centre, Nepean Hospital, Kingswood NSW
[3] Concord Cancer Centre, Concord Hospital, Concord NSW
[4] NHMRC Clinical Trials Centre, Sydney Medical School, University of Sydney, Sydney, Australia
[5] NHMRC Clinical Trial Centre, The University of Sydney, NSW, Australia
[6] Melanoma Institute Australia, The University of Sydney, NSW, Australia

Background: In Australia, 40% of people diagnosed with cancer are of working age (25-64 years). Improvements in cancer treatment have resulted in substantial growth in the costs of care, and patients can bear up to 40% of the out-of-pocket cost of their treatment. Changes in a patient's household income can result in financial burden on patients and their families.

Aim: To provide insight into the financial burden of cancer treatment in patients in the Australian setting.

Methods: We conducted a prospective observational pilot study examining adults treated with anti-cancer therapy in both adjuvant and palliative settings in the outpatient department of a tertiary cancer hospital in Sydney, Australia.

Data was collected using a questionnaire comprising socio-demographic characteristics, employment/income history, health insurance and treatment information; and analysed using descriptive statistics. Six income level categories were derived from mean household annual income data from the Australian Bureau of Statistics, from lowest quintile (less than $25,000) to highest quintile (> $260,000).

Results: Of 31 participants, the median age was 59 years (range 37 - 80 years), 52% females. At time of data collection, 12 patients (39%) were in paid employment. 7 patients were not in any paid employment prior to the diagnosis of cancer (4 retired, 2 unemployed, 1 volunteer). The majority of patients were in full-time jobs (21/31) with others being self-employed (2/31) or in part-time employment (1/31).

Significantly, 30% of patients (9/31) described a reduction in their hours and duties as a result of their cancer diagnosis and treatment. A further 38% (12/31) patients reported they had retired or ceased working during the course of their cancer treatment.

Over half (16/31, [52%]) reported a reduction in their household income level during the course of their treatment. One patient reported an increase in income level due to an inheritance.

Conclusions: This study highlights the significant changes in patients' financial status as a result of cancer diagnosis and treatment. Patient-physician discussions about potential loss of income due to cancer and its treatment are recommended.

Investigation of pyrexia in patients with BRAF V600E/K metastatic melanoma treated with dabrafenib and trametinib.

Hannah Yejin Kim[1], Janna K Duong[1], Georgina V Long[2], Alexander M Menzies[2], Maria Gonzalez[3], Helen Rizos[4], Esther Lim[4], Jenny Lee[4] and Alan V Boddy[1]

[1] School of Pharmacy, University of Sydney, Sydney, NSW, Australia
[2] Melanoma Institute Australia and School of Medicine, University of Sydney, Sydney, NSW, Australia
[3] Melanoma Institute Australia, Sydney, NSW, Australia
[4] Biomedical Sciences, Faculty of Medicine and Health Sciences, Macquarie University, Sydney, NSW, Australia

Background. The combination of a BRAF inhibitor dabrafenib and a MEK inhibitor trametinib (CombiDT) has improved survival outcomes compared with chemotherapy or dabrafenib in advanced BRAF V600E/K melanoma. However, the use of CombiDT has a high incidence of pyrexia (50-70%). Understanding the etiology of pyrexia would maximise the proven benefit of CombiDT therapy.

Aim. To investigate if and to what extent the pharmacokinetics (PK) of dabrafenib and trametinib contribute to pyrexia. To investigate an association between inflammatory cytokines and pyrexia.

Methods. The study included 37 patients with Stage 3 BRAF V600E/K melanoma treated with CombiDT, recruited onto Neo Adjuvant Combi Trial (protocol ID: 200332) between August 2014 to June 2017. Blood samples were collected during the 12 weeks of neo-adjuvant treatment. Plasma concentrations of drugs and metabolites were determined using validated LCMS assays. Population PK model was applied to dabrafenib and trametinib data using NONMEM. A panel of inflammatory cytokines was also measured in patients.

Results. Dabrafenib concentrations ranged from 4.0-4628 ng/ml and trametinib from 1.0-45 ng/ml in 139 (dabrafenib) and 162 (trametinib) post-treatment samples from 34 patients. N-desmethyl-dabrafenib was the most prevalent metabolite, followed by carboxy- and then hydroxy-dabrafenib. A 2-compartment model with first-order absorption provided the best fit to the dabrafenib and trametinib data. Association between pyrexia and higher AUC or C_{min} for the drugs or higher peak metabolite ratio could not be observed from our data. Increase in Interleukin (IL)-1B and IL-6 at early days of treatment (EDT: day 4-7) from baseline were 1.9-fold ($p=0.029$) and 2.5-fold ($p=0.028$) higher respectively in pyrexia group compared to no pyrexia group.

Conclusions. In our study, potential causes of drug-induced pyrexia were investigated. However, apparent relationship between exposure to drugs or metabolites, and pyrexia was not observed. Increase in levels of IL-1B and IL-6 were observed in patients with pyrexia. A high proportion of patients with pyrexia (71%) and only 12% (4 patients) without pyrexia/treatment interruptions were limitations to observing any further apparent relationships between the investigated factors and pyrexia.

FACT binding at MYCN target genes leads to increased transcriptional elongation and MYCN-linked transcriptional activity

Amit Lalwani[1], Daniel Carter[1], Belamy Cheung[1] and Glenn Marshall[1,2]

[1] Children's Cancer Institute
[2] Kids Cancer Centre, Sydney Children's Hospital

Background: Neuroblastoma is a paediatric cancer of the sympathetic nervous system. MYCN amplification occurs in approximately 25% of neuroblastoma patients and is a key indicator of poor prognosis for the disease. Direct targeting of MYCN has been an elusive goal of many cancer drug development efforts but has proven challenging, as MYCN is a largely unstructured protein that lacks deep pockets for drug design. We previously reported that FACT (Facilitates Chromatin Transcription), which is a histone chaperone composed of two subunits; Structure Specific Recognition Protein (SSRP1) and suppressor of Ty 16 (SPT16) regulates MYCN transcriptional activity in a feed-forward manner. FACT inhibition by curaxin compound CBL0137, markedly reduced tumor initiation and progression. However, the mechanisms behind these results and the specific role of FACT in MYCN-driven neuroblastoma oncogenesis remains unclear.

Aim: The main aim is to investigate if FACT has a role in increasing MYCN-driven transcriptional elongation during neuroblastoma onogenesis.

Methods: We employed chromatin immunoprecipitation (ChIP) combined with quantitative real-time PCR to test our hypothesis and to evaluate fold-enrichment of the known binding sites of MYCN, RNA Pol II and H3K27ac, in two MYCN amplified neuroblastoma cell-lines; KELLY and BE(2)C before and after FACT inhibition by CBL0137.

Results: Our preliminary results in both KELLY and BE(2)C cell-lines after FACT inhibition showed reduced enrichment of MYCN binding at the core promoter regions of *ODC1*, *PA2G4* (both critical determinants of MYCN oncogenesis), *SSRP1* and *SPT16* genes. Furthermore, a lower fold-enrichment was also observed at *E2F2* gene promoter region by RNAPII and H2K27ac, suggesting reduced MYCN-driven oncogenesis

Conclusions: FACT is a crucial factor that lies on the crossroads of initiation of RNA Pol II pause release and transcriptional elongation to enhance oncogenic transcriptional and MYCN-linked super enhancer activity. This has important implications for the role of FACT in neuroblastoma and can be expanded into developing novel MYCN-targeted therapeutics.

'I was in a dark place and now I feel alive': Process evaluation of a psychological intervention for melanoma patients

Nadine Kasparian[1,2], Fay Huang[1], Mbathio Dieng[3,4], Frances Rapport[5,6], Phyllis Butow[7], Rachael Morton[3,2], Daniel Costa[8], Scott Menzies[9,10], Graham Mann[11,2] and Anne Cust[4,2]

[1] UNSW Medicine, The University of New South Wales, Sydney, Australia
[2] Melanoma Institute Australia, The University of Sydney, NSW, Australia
[3] NHMRC Clinical Trial Centre, The University of Sydney, NSW, Australia
[4] Cancer Epidemiology and Prevention Research, Sydney School of Public Health, The University of Sydney, NSW, Australia
[5] Australian Institute of Health Innovation, Macquarie University, NSW, Australia
[6] Centre of Healthcare Resilience and Implementation Science, Faculty of Medicine and Health Sciences, Macquarie University, NSW, Australia
[7] Psycho-oncology Co-operative Research Group, School of Psychology, The University of Sydney, NSW, Australia
[8] Pain Management Research Institute, University of Sydney at Royal North Shore Hospital, NSW, Australia
[9] Discipline of Dermatology, Sydney Medical School, The University of Sydney, NSW, Australia
[10] The Sydney Melanoma Diagnostic Centre, Royal Prince Alfred Hospital, NSW, Australia
[11] Centre for Cancer Research, Westmead Institute for Medical Research, The University of Sydney, NSW, Australia

Background: A newly-developed psychological intervention for melanoma patients at high-risk of new primary disease significantly reduced fear of cancer recurrence (FCR) immediately, 6-months, and 12-months post-intervention. Process evaluations are critical to identifying intervention components likely to have had the greatest influence on study outcomes, and optimal models for future implementation.

Aim: To use the Medical Research Council framework for process evaluation to assess intervention reach, fidelity, dose, participant satisfaction, and barriers to implementation.

Methods: Adults with a history of Stage 0-II melanoma were recruited via NSW high-risk melanoma clinics and randomly allocated to the intervention (n=80) or usual care (n=84). Intervention participants received a tailored psycho-educational resource and three individual, telephone-based psychology sessions, scheduled around dermatological appointments. Process evaluation data included participant surveys, intervention delivery processes, and analysis of psychology session audio-recordings against fidelity checklists.

Results: Intervention fidelity was high (88%). Almost all participants (96%) received all intended sessions, and 97% of participants used the psycho-educational resource. Mean combined psychology session duration ('dose') was 1.7 hours (SD=0.9) per participant. Mean satisfaction ratings (out of 10) were 7.9 (SD=2.3) and 7.7 (SD=2.8) for the resource and sessions, respectively (p=0.69). Most helpful resource components (out of 3) were information on melanoma types (M=2.4, SD=0.8) and moles (M=2.4, SD=0.8). Most beneficial tool was the skin self-examination guide, used by 73% of participants. Qualitatively, participants reported a range of intervention benefits, including improved coping and communication. While three participants found discussion of melanoma-related experiences confronting, the majority (81%) would recommend the intervention to others; *"I wish the support was ongoing - not just a study, but a part of our treatment."*

Conclusion: Co-designed in partnership with patients and health professionals, this intervention demonstrated acceptability, feasibility and efficacy in reducing FCR in people with melanoma. Implementation into routine melanoma care is the next vital step.

Detection of immune correlates in cancer patients undergoing immunotherapy using multicolor flow-cytometry.

Puneet Singh[1,2,3], Nirupama Verma[1,3], Kieran Scott[2,3], Bruce Hall[1,3,4] and Paul de Souza[2,3,4]

[1] UNSW
[2] WSU
[3] IIAMR
[4] Liverpool Hospital

Introduction: Immunotherapy in cancer treatment has developed significantly. However, some of the cancers have shown little or no response and even within the known responsive cancers, there is a subset of non-responsive patients. Since immunotherapies act by manipulating and invigorating the patients' immune system, immune correlates are one of the most explored biomarkers for these therapies. In this direction, we developed a multi-colour flow cytometry assay to detect 30 different immune correlates from a single blood draw of 2mL.

Materials and methods: Two 6-antibody panels were and standardized in the peripheral blood collected from healthy donors. This assay was used to analyse the immune correlates in peripheral of cancer patients undergoing immune checkpoint therapy, collected longitudinally at different time points over the course of treatment. The whole blood was stained using the two 6-antibody panels and data was acquired on a BD FACSCanto II (4-2-2 configuration) and analyzed using Flow Jo software v10.2 (Tree Star Inc). Statistical analysis was performed using Graph Pad Prism v7.

Results: The immune cell sub-populations analysed using this method were $CD3^+$, $CD4^+$, $CD4^+$TEMRA, $CD4^+$N, $CD4^+$CM, $CD4^+$EM, $CD8^+$, $CD8^+$TEMRA, $CD8^+$N, $CD8^+$CM, $CD8^+$EM, Tregs, NKT, NK CD56lo and NK CD56hi. Percentage of cells expressing Ki67 was also measured for each one of these populations. Data from healthy controls was analysed to establish a range for each one of these parameters, against which the patient data was compared.

Conclusion: We have developed a liquid biopsy method based on multicolor flow cytometry. This assay can assess a total of 30 different immune correlates from a single blood draw of 2mL in one single experiment. A normal range for various subpopulations in healthy donors was established. Data obtained from the cancer patients receiving immunotherapy show some interesting trends and warrant further validation studies with a larger sample size.

Knockdown of Δ40p53 is associated with reduced EMT and MMP2 protease activity in ZR75-1 breast cancer cells

Xiajie Zhang[1,2], Brianna Morten[1,2], Rodney Scott[1,2,3] and Kelly Kiejda[1,2]

[1] Medical Genetics, Hunter Medical Research Institute
[2] Priority Research Centre for Cancer, School of Biomedical Sciences and Pharmacy, Faculty of Health and Medicine, University of Newcastle
[3] Hunter Area Pathology Service, John Hunter Hospital

Background: Breast cancer is the most commonly diagnosed cancer and remains the second cause of cancer-related mortality among Australian women. The tumour suppressor gene, p53, is not commonly mutated in breast cancer, indicating other mechanisms are involved in compromising the canonical p53 function. The p53 gene can produce not only the full-length protein (p53α) but also 11 smaller isoforms. We have found that Δ40p53 is the most highly expressed isoform in breast cancers, and is associated with worse disease-free survival, suggesting its potential role in metastatic tumour progression and chemotherapy response. Gene set enrichment analysis showed the differently regulated genes between high Δ40p53 vs low delta40p53 are predominantly associated with metastatic processes including epithelial-mesenchymal transition (EMT) and communication with extra cellular matrix (ECM).

Aim: To generate cells with stable knockdown of Δ40p53 and p53α using the breast cancer cell line ZR75-1, and to investigate proliferation, migration, changes of EMT and ECM related markers.

Methods: ZR75-1 cells were transduced with shRNA to knock down either Δ40p53 or p53α. Proliferation, migration assays were performed. Real-time RT-PCR and western blot were used to measure changes on RNA and protein level. Gelatin-zymography was used to quantify MMP2 protease activity.

Results and Conclusions: Following knockdown of Δ40p53, cells proliferated slower and highly aggregated with one another. These cells had a higher level of E-cadherin at the RNA and protein level, migrated slower and had a lower MMP2 activity. In contrast, knockdown of p53α resulted in a mesenchymal-like cell morphology. Cells migrated faster and had a higher MMP2 activity. However, they showed a higher E-cadherin protein level. These results indicate that the full-length p53 plays a predominant role in suppressing EMT, whilst knockdown of Δ40p53 may enhance this function of p53 in the ZR75-1 cells, further suggesting the ratio of Δ40p53:p53 is critical for p53 function.

In-utero exposure to breast cancer systemic treatment: a bi-national study.

Nadom Safi[1], Antoinette Anazodo[2], Alex Wang[1], Zhuoyang Li[1] and Elizabeth Sullivan[1]

[1] University of Technology Sydney, the Australian Centre for Public and Population Health Research (ACPPHR)
[2] Sydney Children's Hospital and Prince of Wales Hospital

Background: The management of cancer diagnosed during pregnancy is challenging, as it requires weighing the benefit to the mother and the potential impact on the growing fetus.

Aim: To examine the effect of in-utero exposure to systemic treatment for breast cancer on the perinatal outcomes of babies born to women with breast cancer diagnosed during pregnancy.

Methods: A bi-national prospective case-cohort study was conducted between 1 January 2013 and 30 June 2014 using the Australasian Maternity Outcomes Surveillance System (AMOSS). Data was collected on babies born to women with a confirmed diagnosis of breast cancer during pregnancy from AMOSS participating hospitals, which represented over 96% of hospitals with eligible maternity units in Australia and New Zealand. The primary outcomes included perinatal death, preterm birth, small for gestational age, neonatal morbidity and congenital malformations.

Results: Thirty-eight babies born to women with breast cancer diagnosed during pregnancy were identified. Of these, 18 babies were exposed to in-utero systemic therapy and 20 were not exposed. The majority of the cases (77.8%) were exposed in the 2nd trimester and 22.2% in the 3rd trimester. In-utero exposure to systemic treatment was associated with significantly higher rates of preterm birth (66.7% vs 20%, P=0.004), and low birthweight (<2500g) (50% vs 0.0%, P=0.001). Eleven of the 12 preterm births followed planned induction of labour or no labour CS (six induced labour and five no labour CS). The indication of planned birth was the management of maternal cancer in seven of the 11 cases. There were no stillbirths, neonatal deaths, or congenital malformations in the study cohort.

Conclusion: There was three times higher rate of preterm birth in babies exposed to systemic treatment in-utero. This was planned preterm birth associated with the underlying indication of maternal cancer management in the majority of the cases.

ONC-212, a novel UPR inhibitor has significant cytotoxic and cytostatic effects against primary CLL cells and cell lines

Narjis Fatima[1], Yandong Shen[1,2], Kyle R Crassini[2], Stephen Mulligan[2], Oliver Giles Best[2] and Richard Christopherson[1]

[1] School of Molecular Biosciences, University of Sydney
[2] Kolling Institute of Medical Research

Translational Significance: As chronic lymphocytic leukemia (CLL) is still considered incurable, research into novel drugs, such as ONC-212 that target leukemic cells within the tumour microenvironment is crucial for improving patient survival rates.

Background: Imipridones with halogen substitutions are cytotoxic against a variety of tumor cell types and inhibit migration of cancer cells through down-regulation of G-protein coupled receptor expression. ONC212 is a recently synthesized analogue of this family of compounds.

We are investigating the therapeutic potential of ONC-212 for CLL. Successful treatment of CLL relies on targeting the leukemic cells within the nodal and marrow tumour microenvironments (TME).

Aims: To evaluate the cytotoxic and cytostatic effects of ONC-212 against primary CLL cells and cell lines under *in vitro* conditions that mimic the TME.

Methods: Primary CLL cells, isolated from the peripheral blood of patients, were co-cultured with CD40-ligand expressing fibroblasts to mimic the supportive effects of the lymph node TME. Using the Crispr/Cas9 technology we generated a *TP53* knock-out OSU-CLL cell line (OSU-*TP53KO*). Cell viability and cycling were assessed using with the mitochondrial dye DiIC1(5), propidium iodide and flow cytometry. Cell proliferation was determined using the amine dye CFSE and flow cytometry.

Results: Primary CLL cells and OSU-CLL cells were sensitive to ONC-212 in a dose-dependent manner. *TP53* knock-out reduced the sensitivity of OSU-CLL cells to ONC-212; IC50 values were 20 and 50 nM for the OSU-CLL and OSU-*TP53KO* lines respectively. ONC-212 also had significant cytostatic effects against OSU-CLL and OSU-*TP53KO* cells, inducing a G1-phase arrest and inhibiting cell proliferation.

Conclusions: Our data suggest that ONC-212 has significant cytotoxic and cytostatic effects against CLL cells within a nanomolar dose range. The efficacy of ONC-212 against CLL cells in fibroblast co-culture and against OSU-*TP53KO* cells suggest the drug may overcome drug-resistance conferred by the TME and defective apoptotic signaling.

Repositioning existing drugs as novel therapeutics for high-risk paediatric leukaemia

Mawar Karsa[1], Angelika Kosciolek[1], Anna Mariana[1], Tim Failes[1], Greg Arndt[1], Ursula R Kees[2], Michelle Haber[1], Murray D Norris[1], Rosemary Sutton[1], Richard B Lock[1], Klaartje Somers[1] and Michelle J Henderson[1]

[1] Children's Cancer Institute Australia
[2] Telethon Kids Institute

Background: Despite remarkable improvements made in the treatment of childhood acute lymphoblastic leukaemia (ALL), prognosis remains dismal for a certain subgroup of high-risk (HR) patients. Development of more effective, less toxic therapeutics is therefore urgently needed.

Aim: The aim of this study was to identify compounds that target HR leukaemia cells based on drug-repurposing, whereby an approved drug is applied to treat a disease other than the one for which it was originally intended.

Methods: A phenotypic screen was performed against HR leukaemia cell lines with a tailored compound library of 3707 approved drugs and pharmacologically active compounds.

Results: The screen identified that two FDA-approved drugs, auranofin and disulfiram, originally developed for treatment of rheumatoid arthritis and chronic alcoholism respectively, had preferential cytotoxicity against leukaemia cell lines compared to solid tumours and normal cells ($p<0.0001$). Both compounds subsequently showed potent activity in paediatric HR leukaemia patient-derived xenograft (PDX) cells *in vitro*, including xenografts derived from *Mixed Lineage Leukaemia*-rearranged ALL and Philadelphia-positive ALL subtypes. The compounds induced apoptosis within 12 hours of treatment through an increase in intracellular reactive oxygen species (ROS) ($p<0.01$), which was accompanied by induction of Nrf2, a master regulator of the antioxidant response. Incubation with ROS scavenger N-acetyl cysteine prior to treatment with either drug prevented the increase in cellular ROS levels ($p<0.05$) and rescued cells from apoptosis ($p<0.0001$). The drugs showed synergy with each other, and Auranofin also potentiated the established chemotherapeutic cytarabine in resistant HR leukaemia cells ($p=0.016$).

Conclusion: In summary, we have identified two FDA-approved drugs that demonstrated potent, synergistic anti-leukaemia activity through ROS induction as well as chemosensitise cells that are resistant to current chemotherapeutics, potentially opening up new avenues for clinical treatment of HR paediatric leukaemia. We are currently testing these therapies *in vivo* using relevant PDX models of HR paediatric ALL.

The advantage of phase-contrast imaging in computed tomography of the breast

Patrycja Baran[1], Seyedamir Tavakoli Taba[2], Yakov Nesterets[3,4], Serena Pacile[5], Susanne Wienbeck[6], Christian Dullin[5,6,7], Fulvia Arfelli[5,8], Sarah Lewis[2], Giuliana Tromba[5], Timur Gureyev[1,2,3] and Patrick Brennan[2]

[1] The University of Melbourne, Australia
[2] The University of Sydney, Australia
[3] Commonwealth Scientific and Industrial Research Organisation, Australia
[4] University of New England, Australia
[5] Elettra - Sincrotrone, Italy
[6] University Medical Center Goettingen, Germany
[7] Max-Planck-Institute for Experimental Medicine, Germany
[8] University of Trieste and INFN, Italy

Background: Propagation-based phase-contrast CT (PB-CT) is an advanced x-ray imaging technique that has capacity to visualise both the absorption and phase contrast (refraction contrast) when x-rays pass through an object. PB-CT is currently achievable using synchrotron radiation, which provides a highly coherent x-ray beam.

Aim: The goal of this study was to compare the radiological quality of images produced by PB-CT technique with images produced by Koning Breast CT (KBCT) system (as an absorption-based CT modality) at the same radiation dose (5.8 mGy).

Methods: Eight formalin-fixed breast tissue samples with various sizes and different types of tumour were prepared for phase-contrast CT and Koning CT imaging. The PB-CT experiment was conducted at the SYRMEP beamline of the Elettra synchrotron in Trieste, Italy and the KBCT scans were collected using a CBCT1000 model machine at the University Medical Center Göttingen, Germany. Six medical imaging experts with at least five years of experience in diagnostic imaging assessed radiological image quality. Four slices per case per modality were presented to the assessors and they were asked to rate overall image quality in each case using a five-point rating scale. Image quality was analysed using visual grading characteristics (VGC) and the bootstrap-averaged area under the curve ($0 \leq AUC_{VGC} \leq 1$) was calculated to measure the difference in the image quality of the two modalities.

Results: Inter-observer agreements (intraclass correlation coefficient) showed good reliability of rating scores; ICC=0.582, CI95%=[0.378, 0.788]. Visual grading analysis revealed that the overall image quality was significantly higher for standard dose PB-CT than standard dose KBCT; AUC_{VGC} =0.990 (p=0.002).

Conclusions: PB-CT can better visualise the weakly absorbing details that are poorly visible in conventional breast CT technique.

Translational significance: PB-CT of the breast is expected to deliver improved image quality compared to current x-ray modalities and become a viable method for early diagnosis of breast cancer in the future.

Investigation of tryptophan metabolism in various human breast cancer subtypes

Ruiwen Benjamin Heng[1]

[1] Macquarie University

Background: Metastasis is the leading cause of death in breast cancer (BrCa). The triple-negative BrCa subtype carries the highest metastasis risk. However, only 18% BrCa patients responded to new immunotherapies. This suggests other mechanism/s assist BrCa to evade these immunotherapies. Considering the many observations linking the kynurenine pathway (KP) to immunosuppression and tumour growth, we hypothesized that the KP may be the major immune modulating mechanism in BrCa development. Interestingly, only a handful of studies have focused on the role of the KP in BrCa. Hence, this study aims to determine KP activity in all BrCa subtypes.

Methods: To understand how KP is regulated in BrCa, we examined the KP profile in seven BrCa cell lines and clinical samples (402 BrCa patients sera and 30 tumour tissues) that represent major subtypes of breast cancer (luminal, HER2, and triple-negative). We carried out qPCR, western blot/immunohistochemistry and ultra-high pressure liquid chromatography on these samples to quantify KP enzyme gene, protein and activity respectively.

Results: Firstly, we found that the KP is dysregulated differently in each BrCa subtype, with most dysregulation observed in triple-negative BrCa patients. Secondly, the downstream KP enzyme's expression and activity was not dependent on rate-limiting IDO1. The third and perhaps most clinically important finding of our study is that the metabolite profile in BrCa patient serum distinguishes triple-negative subtype patients with 90% accuracy.

Conclusion: Our data indicate that KP is dysregulated in all BrCa and may be the major facilitator in the evasion of immune surveillance in triple-negative BrCa. Most importantly, KP metabolite levels in serum may prove to be a valuable biomarker to identify triple-negative BrCa patients.

Translational significance: Our work will highlight the role of KP in BrCa, and potentially identify a new blood-based biomarker to identify triple-negative BrCa patients.

A Novel Molecular Differentiation Score for Hepatocellular Carcinoma Prognosis

Miya John[1], Kyung-Jin Kim[2], Sarah Bae[2], Jacob George[2] and Liang Qiao[2]

[1] Westmead Institute for Medical Research
[2] Storr Liver Centre, Westmead Institute for Medical Research

Background: Hepatocellular carcinoma (HCC) has a dismal prognosis with an overall 5-year survival rate of 3%, partly due to a lack of therapeutic options. Tumor differentiation status is a classical predictor of overall survival in various cancers; however, differentiation-based grading systems primarily rely on qualitative histological attributes lacking in accuracy.

Aim: We sought to develop a novel quantitative molecular score for differentiation that is higher in prognostic accuracy compared to traditional differentiation-based qualitative tumor grading systems.

Methods: Tissue differentiation involves regulation of expression of a specific set of genes that are unique to the cell/tissue type. Hence, a prognostic gene expression signature for liver differentiation by developed and validated by identifying genes that are (a) elevated in the liver (b) differentially expressed prognostic genes in HCC and (c) correlate with tumor grade from public gene expression data.

Results: Among 426 genes elevated in the liver, a panel of differentially expressed genes whose alterations correlate with disease prognosis across multiple HCC datasets was identified and tested for correlation with tumor grade in the TCGA database. A molecular differentiation score for HCC was developed with this differentiation gene signature.

Conclusions: A novel molecular differentiation score was developed for more accurate prediction of HCC tumor grade and prognosis. Additionally, this gene expression signature of differentiation can aid in identifying efficacious therapies for HCC. Moreover, similar strategies can be extrapolated to other cancers.

Translational significance: Currently, there is a lack of molecular classification systems in clinical use for determining prognosis and treatment allocation. The HCC differentiation score developed in this study can be combined with clinical variables to develop a highly accurate prognostic model for HCC which will also aid in better clinical trial designs.

Endothelial niche regulation of normal and malignant haematopoietic stem cells

Ingrid Winkler[1]

[1] Translational Research Institute

Assoc. Prof. Winkler's lab identified a novel role for vascular cell adhesion molecules in promoting the awakening of dormant Haematopoietic Stem Cells (HSCs) in the bone marrow (BM) (Nat Med 2012). Now we show vascular niche adhesion can trigger a cascade of intracellular signalling events that can metabolically and transcriptionally reprogram a cell. For bone marrow (BM) Haematopoietic Stem and Progenitor Cells (HSPC) these newly identified roles open new avenues to tailor immune response and recovery during stress.

Malignant cells also take advantage of these pathways. In malignant cells, aberrant glycosylation associated with oncogenic transformation promotes expression of surface ligands that utilise these pro-survival pathways. The discovery of how cellular adhesion acts to prime leukocytes for appropriate inflammatory response and how this evolutionary-ancient signalling network is hijacked by malignant cells for growth and survival, are the subject of this talk.

Emerging advances in cellular immunotherapy: Immune Correlates to Immune Contexture

Rajiv Khanna[1]

[1] QIMR Berghofer

Complex interactions of different immune cell populations within the tumour microenvironment can impact on progression free survival of cancer patients. Studies carried out in our laboratory have shown that adoptive immunotherapy based on *in vitro* expanded T cells may provide therapeutic benefit for some solid cancer patients. Our studies have also suggested that the clinical response to adoptive immunotherapy may be directly linked to the context-specific phenotypic, functional and transcriptional profile of immune cells in the tumour microenvironment (referred to as immune contexture). Profiling the tumour microenvironment may help us to fully understand how immune infiltrates influence the prognosis. We have developed a validated Opal multiplexed Immunohistochemistry (mIHC) method for immune contexture analysis that allows for automated quantification of phenotype and spatial distribution of different immune cell populations within formalin fixed paraffin embedded tissues. Using integrated mIHC with digital image analysis tools with pattern recognition learning algorithm our study demonstrates the contextual and spatial information of immune subsets with co-expression of checkpoint markers within the tumour microenvironment and its clinical impact on disease progression and response to adoptive T cell immunotherapy. Currently, the response and resistance to immunotherapy for each patient's tumour can be determined long after the patient has commenced treatment. We propose that immune contexture analysis of tumour microenvironment is a useful approach to uncover predictive biomarkers of response as well as resistance to adoptive immunotherapy. Prior knowledge of these resistance mechanisms will have major clinical implication as it can (i) guide the use of an appropriate second-line therapy once resistance begins to develop or (ii) facilitate the use of a frontline combinational therapeutic treatment approach.

The survivorship experiences of Australian Aboriginal and Torres Strait Islander peoples with cancer

Patricia Valery[1]

[1] QIMR Berghofer

Compared to non-Indigenous Australians, Aboriginal and Torres Strait Islander peoples (respectfully referred to here as Indigenous Australians) experience significantly greater morbidity and mortality. This disparity also exists for cancer which affects approximately 1,279 Indigenous Australians each year and is the second leading cause of death for this group. The marked inequalities in cancer mortality and survival for Indigenous and non-Indigenous cancer patients in Australia is largely attributed to being diagnosed later, receiving less treatment, and experiencing higher rates of comorbidities. Many Indigenous Australians face challenges within the health system, namely language barrier, racism, cultural misunderstandings, and emotional, physical, emotional and financial stresses which can affect their cancer outcomes.

While there are many reports about what happens to Indigenous Australians when they are diagnosed and hospitalised with cancer, there is a dearth of information about what happens to Indigenous Australians with a cancer when they are discharged. Our recent program of work addresses some of these gaps. I will present an overview about cancer in Indigenous Australians, and in particular discuss the pattern of care of Indigenous cancer patients in the primary health care setting. I will also talk about the experiences and follow up care of Indigenous people who undergo cancer treatment, and discuss potential action areas to facilitate survivorship from the perspective of Indigenous cancer survivors.

Light and nanotechnology for probing and interacting with biological systems

Ewa Goldys[1]

[1] UNSW Australia

The Australian Research Council Centre of Excellence for Nanoscale Biophotonics draws on key advances of the 21st century, nanoscience, and photonics to help understand life at the molecular level.

This talk will focus on next-generation nanotechnologies developed in our Centre for probing, imaging and interacting with the living systems. These address the key challenges of ultrasensitive detection of key analytes in real environments, molecular complexity, and the requirement for interventions in deep tissue.

Theranostic nanomaterials simultaneously facilitate diagnostics including molecular sensing and active interventions required in therapies. I will discuss how our nanomaterials can produce light and interact with cells when stimulated with high energy radiation, and how this interaction can be quantified. The crossing of length scales inherent in radiotherapy combined with such nanomaterials forms powerful building blocks for innovative cancer treatments.

TNF in anti-tumour immunity and resistance to immunotherapy

Jane Oliaro[1]

[1] Peter MacCallum Cancer Centre

Immunotherapies that enhance cytotoxic T cell activity against tumour cells have revolutionised outcomes for cancer patients. However, patient responses vary widely, and so there is considerable interest in understanding how tumours evade this form of therapy. To investigate this, we carried out a series of CRISPR screens to identify mechanisms of tumour immune evasion from T cell killing. We found that deletion of key genes within the TNF signalling, IFN-amma signalling, and antigen presentation pathways provided protection of tumour cells from T cell killing, and blunted anti-tumour immune responses *in vivo*. Our results also highlighted a role for TNF-mediated bystander killing as a potent T cell effector mechanism that can be enhanced by a class of drugs, called smac-mimetics, that inhibit IAPs and can sensitise tumour cells to TNF-induced cell death. Indeed, our studies showed that the smac-mimetic, birinapant, significantly enhanced tumour cell death in the presence of T cells; an effect that can be amplified upon checkpoint blockade. Taken together, we identify T cell-derived TNF as a potent anti-tumour effector mechanism that can be enhanced with birinapant, and an opportunity for combination therapy through co-inhibition of immune checkpoints.

Real-time precision systems oncology: from leukemias to solid tumors

Olli P Kallioniemi[1]

[1] Karolinska Institute, Sweden and Institute for Molecular Medicine Finland, University of Helsinki

Making cancer care more effective, safe and individually optimized is a key aim for cancer researchers and oncologists worldwide. However, our progress in translating research advances to the clinic is painfully slow, particularly in the current era when 100s of new drugs are being developed for cancer care, and major new tools are available to profile cancers at the genomic, transcriptomic, proteomic, metabolomic, immunological, morphological or single-cell level. The field would need a paradigm shift to be able to make use of the flow of molecular information and the numerous drugs and drug combinations that are becoming available for patient treatment.

Our precision systems medicine strategy is trying to trying to provide answers to these challenges. Precisions systems medicine is based on the integration of genomic, transcriptomic and proteomic profiling data of cancers as well as insights from direct high-throughput ex-vivo testing of *drug* efficacies of a panel of 540 cancer drugs on patient-derived cancer cells. The studies are being performed with a turnaround time of a few days to a few weeks with an attempt to help provide data that could help the oncologist and the patient in real-time. This strategy provides comprehensive, direct information on the drug dependencies of cancers in individual patients.

Our precision systems medicine program was started in acute myeloid leukemias and other hematological malignances and is now being expanded to solid tumors, such as ovarian cancer. This approach can help to reposition existing cancer drugs to new indications, prioritize emerging cancer drugs for clinical testing in molecularly defined subgroups of patients, identify biomarkers and mechanisms of action of drugs as well as help to design tailored drugs and drug combinations for individual cancer patients.

How many cancers might we prevent? Analyses of the preventable burden of cancer in Australia

David Whiteman[1]

[1] QIMR Berghofer

Over the past five decades, epidemiologic and experimental evidence has confirmed that many factors to which humans are commonly exposed cause cancer. Exposure to some causal factors can be modified through intervention, so it is important to estimate the likely effects on cancer incidence if exposure to those factors were reduced to the minimum compatible with optimum health. This presentation will describe the preventable cancer burden, focussing particularly on cancers attributable to tobacco smoke, alcohol, obesity, dietary factors and solar radiation. Projections of future cancer incidence under various scenarios of population interventions will also be described.

Steps towards a comprehensive survey of the proteomic landscape of human cancer

Roger Reddel[1]

[1] The University of Sydney

Proteins have a major role in cellular functions and in determining the behaviour of cells and tissues. Although there have been many informative studies of cancer proteomes over the past two decades, they have all been quite small in scale because of the lack of high-throughput proteomic technologies. This presentation will describe the construction of a laboratory (the ACRF International Centre for the Proteome of Human Cancer [ProCan®]) that has the capacity to generate reproducible proteomics data from many thousands of cancer samples per year, and progress towards the first comprehensive pan-cancer survey of the proteomic landscape of human cancer. This will mostly be a retrospective study of cancer samples for which other 'omic data are already available, from patients where the outcome of treatment is already known. In addition to generating large volumes of data about the biology of cancer, a major focus of the program is searching for proteogenomic signatures that predict response to treatment, to enhance the ability of clinicians to choose the most appropriate treatment for individual cancer patients.

Engaging rural clinicians and patients in translational research: an example in lung cancer

Nicole Rankin[1]

[1] Cancer Council NSW

Background: Lung cancer is the number one cause of cancer death in Australia. There are significant gaps in translation of evidence into practice. In 2012, Sydney Catalyst Translational Cancer Research Centre established an 'evidence into practice' research program across local health districts in Sydney and regional NSW. This presentation will describe how a collaborative relationship was formed with regional and rural stakeholders and will report results across program components.

Methods: Our team selected an overarching implementation science model, the Knowledge to Action Cycle. Guided by the model steps, we utilised various research methods for each component project. We commenced with a scoping review of evidence practice gaps in lung cancer care. We began engagement with stakeholders in Sydney and regional NSW by identifying research priorities (using a modified Nominal Group Technique). To unpack and understand gaps in diagnostic pathways, we conducted qualitative interviews (with patients and general practitioners) and a medical record audit. The culmination was the design and feasibility testing of a tailored intervention (the Referral Decision Prompt) to improve early lung cancer diagnostic referral pathways, which was pilot-tested across three sites.

Results: Research outputs include seven publications in peer-reviewed journals, leveraged funding (over $1M), capacity building (PhD students, international fellowship) and direct impact on clinical practice. We generated new knowledge about the diagnostic pathway, including significant differences for regional and rural patients. Pilot testing of the Referral Decision Prompt had greatest uptake in the regional setting and demonstrated high levels of acceptability with regional clinicians. Our collaboration efforts have helped to drive change in cancer services.

Conclusion: This presentation will reflect on factors that have enabled building a successful collaboration with rural clinicians and patients in NSW.

Targeted Radiotherapy: Current Trends and Future Directions

Paul Keall[1]

[1] The University of Sydney

Radiotherapy is indicated for 48% of cancer patients but current radiotherapy faces a problem: tumours and their surrounding organs move during and between treatments. As a result, radiation beams can be off-target, missing the tumour and striking healthy tissue. This results in reduced therapeutic effectiveness and increased toxicity.

To solve this problem, a new generation of radiotherapy machines is being developed that use images acquired during treatment to guide the therapy. In addition, software-based technologies have been developed to use the capabilities of standard radiotherapy systems to acquire images and adapt the radiation beam to tumour motion during treatment. This presentation will review some of the new technologies that could make image-guided radiotherapy standard practice, both on existing radiotherapy systems and new systems with novel imaging and treatment modalities.

Cervical cancer elimination: When might it be achievable?

Karen Canfell[1]

[1] Cancer Council NSW

Although cervical cancer is one of the most common cancers in women worldwide, it is eminently preventable. The discovery that the human papillomavirus (HPV) is responsible for the large majority of cervical cancers has led to major innovations in HPV prevention, notably the development of prophylactic vaccines against HPV, and HPV DNA-based cervical cancer screening. The World Health Organisation has recently called for global action and coordination to scale up vaccination and screening coverage towards achieving the elimination of cervical cancer. Australia is on track to be the first country in the world to achieve elimination - Australia was the first country to introduce a national publicly-funded HPV vaccination program in 2007, and major effects of HPV vaccination have now been documented in young women at the population level, with substantial reductions in the prevalence of infection with vaccine-included types, in anogenital warts, and in cervical precancerous abnormalities. On December 1st 2017 Australia celebrated another 'world first' with the implementation of a truly integrated approach to vaccination and screening with the transition to primary HPV screening, which is expected to further reduce cervical cancer incidence and mortality by over 20%. A next generation HPV vaccine introduced in 2018, which includes protection against more HPV types, also has further long term implications. This talk will summarise these major transitions in public health in Australia, and discuss the implications for global cervical cancer control. What would it take for these successes to be emulated in low and middle income countries, and what might be the timeframe for achieving elimination in Australia, and globally?

Changing role of imaging in neuro-oncology

Susan Chang[1]

[1] University of California

Overview: Traditional roles of imaging in cancer include the anatomic characterization of tumors and staging. Imaging criteria are also critical in the evaluation of treatments and determination of progression. There are many limitations to the utility on standard imaging in the assessment of patients with glioma. Advanced techniques using metabolic imaging that require a multidisciplinary team of expertise are providing non invasive biomarkers of tumor biology and early response to treatment.

The last decade in cancer research - where we were then and where we are now

Sanchia Aranda[1]

[1] Cancer Australia

The pace of progress in our understanding of cancer is accelerating along with the development of new therapies that challenge received wisdom about the use of traditional treatments such as radiotherapy and chemotherapy. Cancer research and cancer treatment are increasingly centred on predictive and personalised approaches. Predictive medicine increasingly requires real time individual level data to make treatment decisions, yet patients are managed in a health system unable to realise the possibilities that are emerging as our data and decision support systems belong to a bygone era. We are at a cross roads where research investment creates more and more possibilities yet our ability to use them in the clinic falls short and contributes to a widening survival gap between the haves and have nots in our society. This presentation will explore these advances and dilemmas, not from the perspective of science, but from a population viewpoint and from the perspective of an advocacy organisation trying to shape the environment to encourage discovery, shape its focus towards that which will make the most difference and to support policy and practice approaches that support its adoption into the care of patients

Blood based biomarkers for prognosis and monitoring of patients with melanoma

Elin Gray[1]

[1] Edith Cowan University

Background: Current methods of melanoma prognosis are limited to observation of tumour tissue by histology or imaging. The analysis of blood based, tumour specific products, including circulating tumour DNA (ctDNA) and circulating tumour cells (CTCs), can provide a non-invasive approach to assess prognosis, tumour burden and the genetic evolution of tumours in response to therapy.

Methods: We analysed blood samples from melanoma patients before and during treatment with targeted therapies or immunotherapies. ctDNA was analysed by droplet digital PCR based upon identification of somatic mutations in tissue biopsies by next-generation targeted sequencing using a customised panel of 26 melanoma-associated genes. Concurrently, microfluidic devices and multimarker flow cytometry were used to assess CTCs subtypes.

Results: CTCs and ctDNA were detected in 92% and 67% of samples, respectively, prior to treatment initiation. Patients with no, or low, levels of ctDNA and CTCs at baseline had significantly longer PFS. In particular, the presence of PD-L1 positive CTCs was associated with response to PD-1 inhibition. Levels of ctDNA decreased in response to therapy, prior to, or concurrently with radiological response. By contrast, an increase in ctDNA became evident as patients developed resistance to treatment, and in some cases, mutational subclones showed differential response to treatment. Resistance effectors such as NRAS mutations and BRAF-splicing variants were identified in plasma prior to or at the time of clinical progression. In a subgroup of patients that underwent treatment cessation after response to targeted therapy (n=11) or immunotherapy (n=18), ctDNA levels remain undetectable off therapy in all but three cases. The three cases with detectable ctDNA experienced disease progression within weeks of treatment cessation.

Conclusions: Our results highlight the utility of blood based liquid biopsies to assist with prognosis and identification of therapeutic response in metastatic melanoma patients undergoing systemic treatment. In addition, longitudinal ctDNA assessment allows clinicians to monitor treatment response and evaluate dynamic genetic changes. Finally, these results indicate that ctDNA needs to be prospectively analysed to assess whether it can aid in clinical decision making to predict safe cessation of treatment.